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Controlled free-radical polymerization at high pressures : synthesis and properties of poly(α-substituted acrylates).

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CONTROLLED FREE-RADICAL POLYMERIZATION AT HIGH PRESSURES: SYNTHESIS AND PROPERTIES OF POLY(α-SUBSTITUTED ACRYLATES)

A Dissertation Presented

by

JAVID RZAYEV

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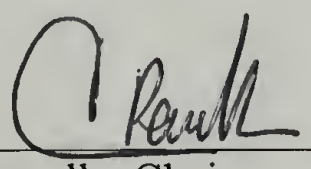

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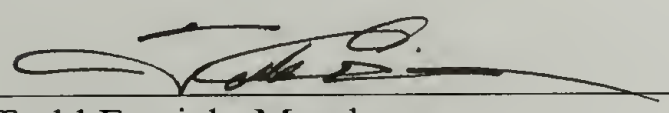

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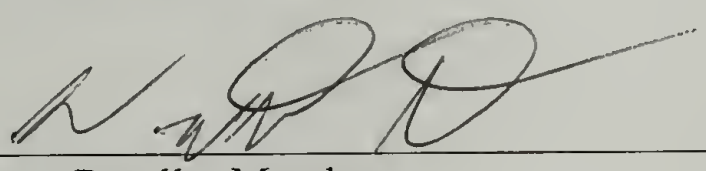

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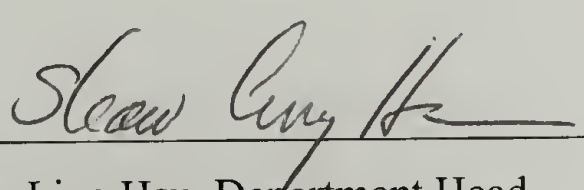

Shaw Ling Hsu, Department Head
Polymer Science and Engineering

DEDICATION

To my parents Zakir and Zenfira.

ABSTRACT

CONTROLLED FREE-RADICAL POLYMERIZATION AT HIGH PRESSURES:

SYNTHESIS AND PROPERTIES OF POLY(α-SUBSTITUTED ACRYLATES)

FEBRUARY 2004

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The free-radical polymerization of a series of α-substituted acrylic acid derivatives has been achieved by using hydrostatic pressure as a kinetic and thermodynamic driving force. It is shown that conducting polymerization in a range of pressures between 1 and 9 kbar dramatically improves the polymerizabilities of the investigated acrylates, opening the way to the synthesis of high-molecular weight polymers in short reaction times. The polymerizabilities of α-alkylacrylates at ambient pressure, obtained by extrapolation from high-pressure kinetic data, correlate well with Meyer's steric parameters for the relevant α-alkyl group. While the polymerization of α-alkylacrylates with linear alkyl groups proceeded via a vinyl double-bond addition in a traditional way, methyl α-isobutylacrylate polymerized though alternating steps of addition and 1,5-hydrogen transfer from the penultimate unit to provide an isomeric α-branched polymer structure.

Structure-property relationships for the synthesized poly(α-substituted acrylates) have been investigated. Increasing the size of the α-alkyl group decreases thermodynamic stability of the poly(α-alkylacrylates), and facilitates their thermal and photo-degradation.

Conformational transitions of poly(α-alkylacrylic acid)s in aqueous solutions are shown to be highly dependent on the size of the α-alkyl group. The transition pH can be fine-tuned by adjusting the total hydrophobic content of the polymer via copolymerization of α-alkylacrylic acid with different alkyl substituents.

A high-pressure reversible addition-fragmentation chain transfer (HP-RAFT) protocol for controlled/living free-radical polymerization has been developed. It is demonstrated that this HP-RAFT technique can be used to livingly polymerize sterically hindered monomers, such as methyl ethacrylate, to provide polymers with low polydispersities, controlled molecular weights and end-groups. A methodology for the synthesis of well-defined poly(ethacrylic acid) has been developed.

The controlled polymerization of polystyrene-methacrylate macromonomers has been achieved by HP-RAFT, providing densely branched comb-like polymers with controlled molecular weight characteristics. The synthesis of linear-comb diblock copolymers is also achievable by this technique.

The HP-RAFT polymerization of traditional monomers, such as methyl methacrylate (MMA), has been investigated. It is demonstrated that the methodology allows for the synthesis of ultra-high molecular weight polymers with low polydispersities. The technique was used to obtain well-defined PMMAs with molecular weights of more than one million.

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CHAPTER 1

INTRODUCTION

Background

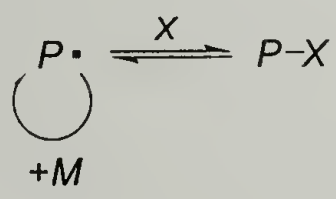
The synthesis of well-defined polymers is a major goal of polymer chemistry. Control of molecular weights, molecular weight distributions, chemical structure of the end-groups, stereochemistry, branching patterns, and other architectural characteristics has been the focus of many research efforts. With an increased interest in nanotechnology, a need for polymeric materials with well-controlled characteristics has become more relevant than ever. Developing materials for nanoscale assembly or for use in biomedical applications requires precise control of the polymeric structure. Living polymerization techniques are indispensable tools for this purpose. By minimizing the amount of undesired reactions such as termination and chain-transfer, living techniques make possible the synthesis of polymers with controlled molecular weights, narrow molecular weight distributions, and well-defined end-groups. They also provide a route to more complex polymeric architectures, such as block and star copolymers.

After it was realized in the 1950s that anionic polymerization could be used for that purpose,[1] living anionic polymerization became a technique of choice for the synthesis of well-defined polymers.[2,3] The impossibility for charged propagating species to terminate by bimolecular coupling, in contrast to free-radical intermediates, is one of the key features that allow anionic polymerizations to exhibit a truly living character. However, highly reactive anionic species have a number of drawbacks, such as a high sensitivity towards common impurities and moisture, intolerance to many functional groups, and a

frequent need for low temperatures, a costly endeavor. These features not only limit the type of materials that can be synthesized in a controlled fashion, but also make it difficult and expensive to implement relevant processes at the industrial scale.

Living free-radical polymerization (LRP) techniques emerged in the 1980s[4] and underwent an explosive growth in the 1990s as an alternative to anionic techniques.[5] A key feature of LRP is the fast equilibrium between active $P\cdot$ and dormant $P\text{-}X$ species, which maintains a low concentration of free-radical species, while allowing all the polymer chains to grow at the same time (Scheme 1.1). A number of LRP protocols have been introduced, for example nitroxide-mediated radical polymerization (NRP),[6] atom-transfer radical polymerization (ATRP),[7,8] and reversible addition-fragmentation chain-transfer (RAFT) polymerization.[9] Based on the same central concept, these methods differ in the mechanism underlying the equilibrium depicted in Scheme 1.1. For example, NRP relies on the reversible termination of active polymer chains with a stable nitroxide free-radical, ATRP uses redox chemistry to switch between end-capped dormant halides and active radical species, and RAFT is based on a direct chain-transfer between dormant and active chains. Each protocol has its own advantages and limitations, best suited for selected families of monomers.

Scheme 1.1 The equilibrium between dormant and active species.



Due to their free-radical nature, LRPs have a superb tolerance to most functional groups and also to moisture. In the past two decades, many new functional polymers

with well-controlled structural characteristics have been synthesized by LRP techniques.[10] Among the monomers successfully polymerized, styrene and (meth)acrylate derivatives share the lion's part. Some limited success has also been achieved for other monomers, including conjugated dienes, acrylamides, vinyl pyridines, acrylonitrile, and vinyl acetate.

Despite these achievements, LRP techniques suffer from a few major limitations, which all originate from the fact that the livingness in these systems is achieved by lowering the concentration of free radicals.[11] Low concentrations of active free-radical species result in very low polymerization rates, much lower than for the equivalent uncontrolled polymerizations. Under such conditions, it becomes impossible to obtain high-molecular weight polymers within a reasonable timeframe, or to polymerize monomers of low polymerizability in a living fashion. Most of the polymers prepared from small monomers by LRP techniques have molecular weights well below 100,000 $g \cdot mol^{-1}$, with the upper values around 200,000 $g \cdot mol^{-1}$.[6,8] Some sterically hindered monomers, which can still be polymerized slowly by traditional, uncontrolled free-radical polymerization conditions, cannot be polymerized under LRP conditions.

Goal and Motivations

The ultimate goal of this dissertation is to develop a living polymerization methodology that can circumvent the inherent limitations associated with the slow rates typical of traditional LRP techniques, and by doing so, to design reasonable routes to polymers that are either impossible to obtain or too expensive to synthesize using existing methodologies. Section I will focus on the polymerization of sterically hindered monomers in a living fashion. This will broaden the scope of LRP, and allow for the

synthesis of new functional polymers. Section II targets the living polymerization of traditional, easily polymerizable monomers such as methyl methacrylate, so that very high molecular weight polymers can be obtained without loss of the living character of the polymerization. Well-defined high-molecular weight polymers are important for expanding the size range available for nanostructured materials. "Large"-size nanostructures have already found use in applications such as photonic band-gap materials, nanostructured morphologies based on block copolymers, and in the design of compatibilizing agents for high mechanical performances.[12-14]

Experimental Strategy

As mentioned earlier, "livingness" in LRP is achieved by controlling a delicate balance between propagation and termination that maintains low concentrations of free-radicals. While termination, a diffusion-controlled process, can never be fully prevented, the concentration of propagating free-radical species in LRP is lowered until the rate of bimolecular radical termination becomes negligibly small relative to the rate of propagation. Unavoidably, this very low concentration in propagating species results in a decrease in the rate of polymerization R_p, which is directly proportional to the concentration of active free-radicals according to the following kinetic equation:

$$R_p = k_p[R\cdot][M] \qquad (1.1)$$

where $[R\cdot]$ is the concentration of propagating free-radicals, M is the monomer concentration, and k_p is the rate coefficient for propagation.

In order to increase the rate of LRPs, one of the three parameters on the right-hand side of Equation 1.1 has to be increased. Specifically, one can attempt to:

(a) Increase [M] : Since the upper concentration of liquid monomers [*M*] is limited by the liquid bulk density, and most polymerizations are already conducted in bulk or high concentrations (> 1 $mol{\cdot}L^{-1}$), this parameter is already at or close to its maximum value.

(b) Increase [*R*·] : A low concentration of free-radicals [*R*·] has to be maintained throughout the polymerization to favor propagation *vs*. termination. As the optimum value depends on the actual value for the termination rate coefficient k_t, experimental conditions can in many instances be identified in order to obtain lower values for k_t (e.g. high viscosity), allowing higher concentrations of propagating free-radicals to be used, and leading to faster polymerizations without jeopardizing the living character of the polymerization.

(c) Increase k_p : Another way of accelerating the polymerization is to increase the propagation rate coefficient k_p, which is influenced by the nature of the monomer and – to a much lower extent – by the surronding environment (solvent polarity and viscosity). It can also be significantly modified by changing temperature or pressure. Out of these tow variables, temperature is of little help as side reactions become predominant at temperatures higher than those used traditionally, leading to chain-transfers. From a thermodynamic point of view, raising the temperature is also problematic in the case of monomers with low ceiling temperatures (defined as the equilibrium temperature above which the polymerization becomes thermodynamically impossible).[15]

Here we hypothesize that hydrostatic pressure (in the range of several kilobars) can be used to achieve the desired selectivity, and alleviate problems associated with the slow

rate typical of LRPs at ambient pressure. Pressure influences the rates of elementary reactions according to Equation 1.2:[16]

$$\frac{d \ln k}{dP} = -\frac{\Delta V^{\ddagger}}{RT} \qquad (1.2)$$

where k is the rate coefficient, $\Delta V^{\ddagger}$ is the activation volume of the reaction, P is the pressure and R is the gas constant. It is well-established that hydrostatic pressure increases the rate of propagation for vinyl monomers and lowers the rate of free-radical bimolecular termination. The decrease in the rate of termination, a fast process that is often diffusion-limited, results from the increase in viscosity associated with higher pressures. Although chain transfers could theoretically also be accelerated by using higher pressures, the value of the chain transfer constant (ratio between k_p and k_t) is often unaffected as both chain-transfer propagation have similar activation volumes.

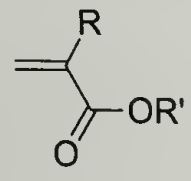
Pressures are also known to favorably affect propagation-depropagation equilibria, and consequently to increase the ceiling temperature T_c.[15] Therefore, polymerizations thermodynamically not feasible under ambient conditions become possible at high pressures. The increase of T_c with pressure is governed by Equation 1.3, and depends on the heat and volume changes of polymerization (ΔV and ΔH, respectively). For polymerization of most vinyl monomers, both of these terms are negative, which results in an increase of T_c with pressure.

$$\frac{d \ln T_c}{dP} = \frac{\Delta V}{\Delta H} \qquad (1.3)$$

As monomer targets in our studies, we will focus on α-substituted acrylates (Scheme 1.2), a versatile family of acrylic monomers having two structurally tunable functional groups per monomeric unit, with methyl methacrylate (MMA, R = R' = methyl) being

the most common representative. The rationale for our choice is discussed in the following section.

Scheme 1.2 α-Substituted acrylates.



α-Substituted Acrylates

Acrylic monomers have found widespread use in industry and academic research. Countless number of polymeric materials based on acrylic structures have been synthesized and characterized, with some of them integrated into our everyday lives via a wide range of applications. A highly polymerizable double bond and a reactive versatile ester functionality provide this class of monomers with both structural versatility and reasonable reactivity under free-radical and/or anionic polymerization conditions. Acrylic monomers have been explored extensively by polymer chemists seeking novel functional materials based on a simple, well-characterized backbone.

Most of the derivatives have been obtained by modification of the ester group, and the structure-property relationships for the relevant polymeric systems have been well investigated.[17] An alternate approach involving the functionalization of the acrylate via a modification of the substituent located on the α-position has been quite rare, and very few examples can be found in the literature[18] (noticeable exceptions include the methacrylate family, with a simple methyl group as α-substituent, α-cyanoacrylates (super glue), and α-chloroacrylates).

α-Substituted acrylates (Scheme 1.2) are superior to simple acrylates in that they display two different functionalities on a single monomeric unit. This additional versatility becomes an essential prerequisite in a number of applications. For example, in coatings, one of the functionalities can be used as a crosslinker while the other can be used to adjust the physical and chemical properties of the polymeric material (e.g. adhesion, biodegradability).[19] Two or more distinctly different functional groups of a hydrophilic or hydrophobic nature are also necessary to provide polymeric systems with amphiphilic characteristics, an important feature in many bio-related applications. In addition, even simple α-substituents, such as alkyl groups, can have a significant effect on solid-state polymer properties such as the glass transition, or the thermal and photo-stability.

Despite all these prospective advantages, α-substituted acrylates have not found widespread use, largely because of their poor polymerizabilities.[18] It has long been known that the size of α-substituents on acrylate monomers affects both the thermodynamics and kinetics of the polymerization. Thermodynamically, the steric strain arising from interactions between bulky neighbors on the polymer backbone decreases the exothermicity of the polymerization, and consequently the ceiling temperature T_c. Kinetically, bulky α-substituents slow down the propagation step, and decrease the monomer's overall polymerizability. Even minimal change in the size of the α-substituent can have a significant impact on the polymerizability. For example, methyl ethacrylate (MEA) with an ethyl group in the α-position displays a much lower polymerizability than methyl methacrylate (MMA) with an α-methyl group. While MMA is a highly polymerizable monomer with a k_p equal to 510 $L \cdot mol^{-1} \cdot s^{-1}$ at 60 °C [20]

and a T_c higher than 200 °C, MEA has a k_p of 8.6 L·mol^{-1}·s^{-1} (60 °C) [21] and a T_c of 82 °C,[22] and as a result polymerizes slowly to a low molecular weight polymer under typical free-radical polymerization conditions. Acrylates with α-alkyl groups larger than an ethyl are even more reluctant to polymerize. Previous attempts to polymerize these monomers resulted either in low molecular weight oligomers and low rate of polymerization, or no polymer being recovered at all.[23-25] For acrylates with *n*-alkyl α-substituents, moderate molecular weight polymers can be obtained by polymerization of the corresponding acids and subsequent methylation.[26]

We have been interested in α-substituted acrylates for possible use of the corresponding polymers in lithographic and nano-templating applications (R = bulky alkyl), biomedical research (R = alkyl, R' = H), as well as for the preparation of nano-objects (R' = polymer). The reasons why these polymers offer distinct advantages with respect to more traditional systems will be revealed in detail throughout this thesis.

Dissertation Plan

The dissertation is divided into two principal sections. Section I deals with the uncontrolled free-radical polymerization of α-substituted acrylates under high-pressure conditions. It was important to establish the free-radical polymerizability of these monomers under high pressure before attempting their living/controlled polymerization. Section I also describes some interesting properties of the obtained polymers. In Chapters 2 and 3, kinetic and mechanistic investigations on the polymerization of α-alkylacrylates under high pressure are presented. Chapter 4 summarizes our efforts in the characterization of the thermal properties and degradation behavior of poly(methyl α-

alkylacrylates). Chapter 5 deals with the synthesis and characterization of amphiphilic polymers obtained from α-alkylacrylic acids. Chapter 6 describes our results on the polymerization behavior of functional α-substituted acrylates derived from Baylis-Hillman adducts.

Section II covers our research efforts in the living free-radical polymerization of α-substituted acrylates under high pressure. The living polymerization of sterically hindered monomers, as well as the controlled synthesis of high molecular weight polymers from traditional monomers, are described. Chapter 7 deals with the kinetic and mechanistic investigations of the RAFT polymerization of methyl ethacrylate under high pressure. Chapter 8 describes the synthesis of well-defined poly(ethacrylic acid). Chapter 9 is devoted to the controlled synthesis of high-molecular weight poly(methyl methacrylate) of narrow molecular weight distribution. Finally, in Chapter 10 some initial results on the living polymerization of methacrylic macromonomers are rapidly presented.

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CHAPTER 2

POLYMERIZATION OF STERICALLY CONGESTED α-ALKYLACRYLATES UNDER HIGH PRESSURE

Introduction

Acrylic monomers are among the most versatile monomers used in academic research and industry. Over the years, many acrylate derivatives with different side groups on the ester position have been synthesized and polymerized, resulting in a large variety of polymeric materials. Such versatility has made it possible to develop a detailed understanding of the effect of ester substituents on polymer properties.[1] Using this knowledge, many new polymer structures with predefined characteristics have been obtained. Despite a great diversity achieved through variations on the ester side group, only a limited number of acrylates with substituents in the α-position have been studied in detail, with the exception of methacrylate systems. Polymers from acrylates with α-substituents larger than a methyl are, in particular, quite rare, the major obstacle in their development being their often poor polymerizability.[2] Side groups in the α-position have a much greater impact than ester substituents on the acrylate polymerizability because of the closer proximity to the propagating free-radical center. Although the main reason for the low polymerizability observed in α-substituted acrylates is the steric hindrance of the α-substituent, the overall influence of the α-substituent on the polymerizability of acrylates is rather complex and usually unpredictable. Depending on the nature of the α-substituent, an acrylate can polymerize easily to a high polymer despite the bulkiness of the α-substituent,[3] undergo addition-fragmentation[4] or be reluctant to polymerize at all.[5]

We have become interested in α-alkylacrylates from both theoretical and practical perspectives. Alkyl groups can serve as a model of purely steric interactions, and thus can be used to evaluate the steric influence of the α-substituent on the polymerizability of acrylates. At the same time, it is known that in the absence of polar effects, increasing the size of α-substituent will diminish the ceiling temperature of the monomer. Thus, polymers with progressively decreasing ceiling temperatures could be obtained. These metastable, i.e. thermodynamically unstable but kinetically locked, polymers may undergo facile thermal and photo degradation and so can be potentially used in applications where enhanced degradability is desired, such as photolithography or nanotemplating.

In this chapter, the free-radical polymerizability of a series of α-alkyl acrylates with increasing steric congestion was investigated in an attempt to analyze in detail the steric effects exerted by the α-substituent on the polymerizability. For the polymerization of these traditionally "non-polymerizable" systems, several kinetic and thermodynamic barriers had to be overcome, and this was accomplished by using high-pressure conditions.

Experimental Section

Materials. Dimethyl ethylmalonate was obtained from Fluka; all other chemicals were purchased from Aldrich. 2,2'-Azoisobutironitrile (AIBN) was recrystallized from methanol. Methyl ethacrylate was synthesized according to a previously reported procedure.[6]

Synthesis of Dimethyl Alkylmalonates. A classical procedure for the alkylation of malonic ester was adapted for the synthesis of dimethyl alkylmalonates: after the

dissolution of metallic sodium (0.25 moles) in 125 mL of anhydrous methanol, dimethyl malonate (0.256 moles) was slowly added. Alkyl bromide (or isopropyl iodide) (0.25 moles) was slowly added, and the mixture was refluxed overnight. The solvent was evaporated, and the residue treated with 75 mL of water and extracted with ether (3×100 mL). The organic phase was dried over $MgSO_4$, the ether was then evaporated and the residue was distilled at reduced pressure:

Dimethyl *n*-butylmalonate. b.p. 78-80 °C at 4 Torr. Yield: 72%.

Dimethyl *iso*butylmalonate. b.p. 101-103 °C at 15 Torr. Yield: 70%.

Dimethyl *n*-propylmalonate. b.p. 77-79 °C at 7 Torr. Yield: 71%.

Dimethyl *iso*propylmalonate. b.p. 65-69 °C at 3 Torr. Yield: 67%.

Synthesis of Methyl α-Alkylacrylates. The following general procedure was used for the synthesis of the methyl α-alkylacrylates. KOH (11.6 g in 70 mL of methanol) was added dropwise to a solution of dimethyl alkylmalonate (0.176 moles) in methanol (50 mL) at 0 °C. The mixture was stirred for 5 hours at 0 °C. Methanol was evaporated, the white solid residue was dissolved in 70 mL of water and acidified with concentrated hydrochloric acid. The mixture was extracted with diethyl ether (3×60 mL) and dried over $MgSO_4$. The product, methyl alkylmalonic acid, was obtained by evaporating the ether and was used in the next step without further purification (yield > 95%).

Diethyl amine (0.055 moles) and formaldehyde (0.11 moles, 37 wt % solution in water) were added slowly to methyl alkylmalonic acid (0.0548 moles). After refluxing overnight, the mixture was cooled down, a solution of K_2CO_3 (0.81 g) in 5 mL of water was added, and the resulting mixture was extracted with ether. The organic phase was

washed with 4.25 mol·L^{-1} sulfuric acid and then with water and finally dried over $MgSO_4$. The solvent was evaporated, and the residue distilled under reduced pressure.

Methyl α-propylacrylate (M*n*PA). bp 68-70 °C at 61 Torr. Yield: 58%. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.92 (t, J = 6.7 Hz, 3H), 1.49 (m, 2H), 2.28 (t, J = 7.6 Hz, 2H), 3.75 (s, 3H), 5.52 (s, 1H), 6.14 (s, 1H).

Methyl α-*iso*propylacrylate (M*i*PA). bp 61-63 °C at 51 Torr. Yield: 53%. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 1.09 (d, J = 6.8 Hz, 6H), 2.81 (sept, 1H), 3.76 (s, 3H), 5.53 (s, 1H), 6.12 (s, 1H).

Methyl α-butylacrylate (M*n*BA). bp 76-77 °C at 40 Torr. Yield: 73%. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.91 (t, J = 7.2 Hz, 3H), 1.40 (m, 4H), 2.29 (t, J = 7.2 Hz, 2H), 3.74 (s, 3H), 5.52 (s, 1H), 6.12 (s, 1H).

Methyl α-*iso*butylacrylate (M*i*BA). bp 82-84 °C at 83 Torr. Yield: 55%. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.89 (d, J = 6.4 Hz, 6H), 1.79 (m, 1H), 2.18 (d, J = 7.0 Hz, 2H), 3.75 (s, 3H), 5.50 (s, 1H), 6.16 (s, 1H).

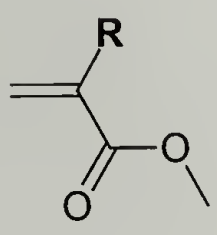
Polymerizations at High Pressure. Polymerizations were carried out in 2 mL Teflon ampoules in a high-pressure reactor purchased from the High Pressure Research Center of the Polish Academy of Sciences. The equipment included a hydraulic press model LCP20 and a pressure reaction vessel equipped with a temperature controller. Monomers were deoxygenated by bubbling with nitrogen for 10-15 minutes prior to polymerization. The polymers were precipitated in hexane (either directly from the polymerization mixture or after dilution with tetrahydrofuran) and dried *in vacuo*. Yields were determined gravimetrically.

Measurements. Molecular weights of the polymers were determined by gel permeation chromatography (GPC) with a PL LC 1120 pump, Waters R403 Differential Refractometer detector, and three PLgel columns (10^5, 10^4, and 10^3 Å). The system was calibrated with 13 poly(methyl methacrylate) standards. ^{1}H NMR spectra were recorded on a 300 MHz Bruker DPX spectrometer.

Results and Discussion

High Pressure Polymerizations. Acrylates with α-ethyl, -*n*-propyl, -*iso*propyl, -*n*-butyl and -*iso*butyl groups (Scheme 2.1) have been polymerized in bulk at 65 °C at pressures ranging from 1 to 9 kbar. Representative examples are shown in Table 2.1. Large variations in the rate of polymerization required the use of different initiator concentrations at different pressures in order to keep reaction times within a reasonable range. High molecular weight polymers were obtained from every monomer except M*i*PA, which contains a very bulky isopropyl group and was reluctant to polymerize even at 9 kbar. This is in agreement with the results reported by Holmes-Walker et al. that only dimerization of methyl α-*tert*-butylacrylate could be observed at 10 kbar (100-130 °C, bulk, 6.2 mol% BPO).[7]

Scheme 2.1 Methyl α-alkylacrylates.



Acrylate	R
MMA	$-CH_3$
MEA	$-CH_2CH_3$
M*n*PA	$-CH_2CH_2CH_3$
M*i*PA	$-CH(CH_3)_2$
M*n*BA	$-CH_2(CH_2)_2CH_3$
M*i*BA	$-CH_2CH(CH_3)_2$

Polymers were obtained as white powders after precipitation in hexane. Analysis by ^{1}H NMR confirmed the expected structure $(CH_2\text{-}C(R)COOCH_3)_n$ for all the polymers but poly(M*i*BA). An in-depth NMR characterization of the polymers obtained from M*i*BA and an elucidation of its polymerization mechanism will be presented in the following chapter. Relative molecular weights and molecular weight distributions of the polymers were determined by GPC using PMMA standards. Representative results are included in Table 2.1. As expected, much higher molecular weights can be obtained by using high pressure. The evolution of M_n with pressure is in general agreement with the kinetic data.

Table 2.1. Polymerization results for α-alkylacrylates at high pressure[a]

Monomer	[AIBN]	Pressure (kbar)	Time (min)	Conversion (%)	M_n[b] ($\times 10^{-3}$)	$\frac{M_w}{M_n}$ [b]
MEA	0.167	0.001	900	10.5	1.8	1.60
	0.167	1	240	11.1	-	-
	0.167	3	45	10.1	-	-
	0.0418	5	20	6.7	68.6	2.22
	0.0165	6	25	9.0	-	-
	0.0166	7	16	9.3	-	-
	0.00824	9	10	7.7	138.6	3.61
M*n*PA	0.0355	5	35	11.5	149.3	2.37
M*i*PA	0.149	5	720	6.0	-	-
	0.00853	9	840	4.9	8.4	1.28
M*n*BA	0.167	3	45	11.6	-	-
	0.0318	5	20	7.34	138.1	2.90
	0.0152	6	27	13.3	-	-
	0.0166	7	15	13.3	-	-
	0.00647	9	10	9.0	-	-
M*i*BA	0.0418	5	360	13.4	39.9	1.61
	0.0418	7	90	8.6	-	-
	0.0426	8	83	10.5	-	-
	0.0418	9	45	9.2	179.4	2.69

[a] $T = 65$ °C, bulk monomer
[b] GPC (PMMA standards)

Initial rates of polymerization were calculated from gravimetric results. Given the short reaetion times used in this study and the slow rate of decomposition for initiator at high pressures, the initiator eoncentration can be safely assumed to be eonstant. For the control experiments eonducted at atmospheric pressure, the rate of polymerization was ealculated aceording to Equation 2.1, which takes into account the decrease in initiator eoncentration over time.[6]

$$R_p = \frac{k_d \Delta[M]}{2(e^{k_d t/2} - 1)} \qquad (2.1)$$

Under traditional free-radieal polymerization kinetics, the overall polymerizability of a monomer ean be measured by the ratios expressed in Equation 2.2, where the left hand of the equation refers to measurable variables and the right hand is a ratio of rate eoefficients for propagation (k_p) and termination (k_t) multiplied by a constant ($k_d^{1/2} f^{1/2}$) typical of the initiator.

$$\frac{R_p}{[M][I]^{1/2}} = \frac{k_p\, k_d^{1/2}\, f^{1/2}}{k_t^{1/2}} \qquad (2.2)$$

In the applied kinetic scheme, the rate of chain transfer to monomer was neglected. Although the chain transfer constants to monomer for the studied α-alkylacrylates have not been measured, they are not expected to be much different from the very low value reported for MMA (2×10^{-5} at 65 °C and 1 atm.).[8]

The influence of pressure on $\ln(R_p\,[M]^{-1}\,[I]^{-1/2})$ for MEA, M*n*BA, M*i*BA and M*i*PA is shown in Figure 2.1. M*n*PA showed a kinetic behavior similar to M*n*BA and was not studied in much detail. In the high pressure regime (≥ 3 kbar), $\ln(R_p\,[M]^{-1}\,[I]^{-1/2})$ for MEA and M*n*BA first increased linearly, then gradually leveled off at higher pressures. This last feature can be attributed to the change in activation volume at very high

pressures, a behavior which has been observed for other monomers.[9] From the linear region (3-7 kbar), overall activation volumes ($\Delta V^{\ddagger}_{over}$) for MEA and M*n*BA were estimated to be -14.9 and -17.0 mL·mol^{-1}, respectively. For M*i*BA and MiPA, increase in $\ln(R_p [M]^{-1} [I]^{-1/2})$ throughout the investigated region (5-9 kbar) resulted in $\Delta V^{\ddagger}_{over}$ values of -11.6 and -7.5 mL·mol^{-1}, respectively. Values for overall activation volumes are summarized in Table 2.2 along with other kinetic and structural parameters. It should be mentioned that $\Delta V^{\ddagger}_{over}$ values obtained in this work for α-alkylacrylates are in the same range as those reported for MMA polymerization. Direct comparison with literature values reported for MMA and methyl acrylate is difficult due to the dependence of $\Delta V^{\ddagger}_{over}$ on polymerization temperature and initiator.

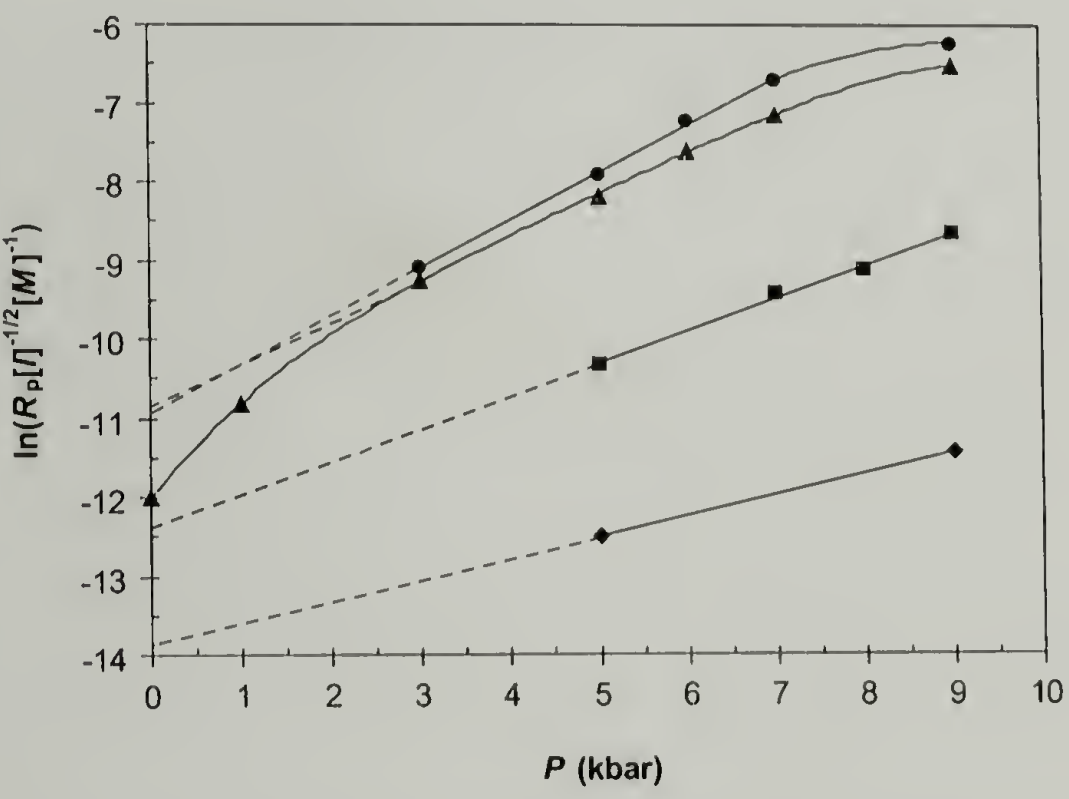


Figure 2.1. Polymerizability factor as a function of pressure for methyl α-alkylacrylates (65 °C, bulk, AIBN): MEA(▲), M*n*BA(●), M*i*BA(■), M*i*PA(◆).

As expected, the activation volume for M*n*BA, a more sterically hindered monomer, is higher than that for MEA. However, the activation volume for M*i*PA is unexpectedly low, which probably results from the different effects of pressure on the propagation and

termination steps. Overall activation volumes for a free-radical polymerization result from a combination of activation volumes for individual steps in the chain reaction that can be represented by:

$$\Delta V^{\ddagger}_{over} = \Delta V^{\ddagger}_{p} - \frac{1}{2}\Delta V^{\ddagger}_{t} + \frac{1}{2}\Delta V^{\ddagger}_{i} \qquad (2.3)$$

where $\Delta V^{\ddagger}_{p}$, $\Delta V^{\ddagger}_{t}$ and $\Delta V^{\ddagger}_{i}$ are the activation volumes for propagation, termination and initiation, respectively. The contribution of the initiation term is identical for all monomers and does not affect the comparison. Previous studies on the effect of pressure on propagation for (meth)acrylates indicate that $\Delta V^{\ddagger}_{p}$ is larger for methacrylates than for acrylates,[11-13] which is consistent with the general observation that more sterically hindered reagents usually have larger activation volumes. This can also be expected to hold for the highly sterically hindered α-substituted acrylates investigated here.

Table 2.2. Kinetic parameters for the polymerization of α-alkylacrylates[a]

Monomer	$-\Delta V^{\ddagger}_{over}$ ($mL \cdot mol^{-1}$)	$k_{pol} \times 10^3$ ($L^{1/2} \cdot mol^{-1/2} \cdot s^{-1/2}$)	$V^{a} \times 10^2$ (nm^3)[b]
MMA	–[c]	76.5	2.84
MEA	14.9	5.5	4.31
M*i*PA	7.5	0.3	5.74
M*n*BA	17.0	5.0	4.79
M*i*BA	11.6	1.2	5.26

[a] T = 65 °C
[b] Steric factors for the α-substituent[10]
[c] Not determined

While the influence of pressure on propagation is more or less straightforward, its effect on termination can be rather complex.[9] Pressure can be expected to slow down the diffusion of macroradicals, but accelerate their recombination in the solvent cage. When recombination reactions between the radicals are diffusion-controlled, the effect of

pressure on termination will be similar to the effect of pressure on diffusion. Lower values for k_t can be expected, which will favorably affect the overall polymerizability. Buback et al. recently proposed, based on earlier results by Russo and Munari, that steric hindrance may play an important factor in the termination reactions for some monomers.[14,15] Within that framework, it can be envisioned that pressure possibly increases the termination rate, as it is usual for bimolecular reactions, by facilitating access to the sterically crowded transition state. We suggest that one possible explanation for the low $\Delta V^{\ddagger}_{over}$ value observed for M*i*PA can be related to the influence of pressure on $\Delta V^{\ddagger}_{t}$.

These findings suggest that the overall influence of pressure on free-radical polymerizability could be more complex than what can be inferred from experimental studies obtained on "normal" monomers such as styrene and MMA. It also indicates that for sterically congested monomers, high pressure will not always benefit the overall polymerizability; after some steric crowding is reached, the negative influence exerted on the termination step might overcompensate for the beneficial influence exerted on the propagation step resulting in an overall decrease in polymerizability.

A deviation from linearity in the lower end of high-pressure region (studied only for MEA) was also observed, which can be attributed to the ceiling temperature effect. For polymerizations carried out at the lowest pressures (ambient pressure and 1 kbar), T_c is probably close to the polymerization temperature (65 °C), meaning that depropagation also affects the polymerizability. By extrapolation from the linear region, the overall polymerizability ($R_p [M]^{-1} [I]^{-1/2}$) at atmospheric pressure can be estimated to be 1.99×10^{-5} $L^{1/2}\cdot s^{-1}\cdot mol^{-1/2}$, a substantially higher number than the experimentally obtained

value of 6.09×10^{-6} $L^{1/2}\cdot s^{-1}\cdot mol^{-1/2}$. The difference between the two can be used to evaluate the propagation-depropagation equilibrium. When the polymerization temperature is close to T_c, the rate of polymerization can be expressed as $R_p' = (k_p[M]-k_{dep})[P\cdot]$, where k_p and k_{dep} are the rate coefficients for propagation and depropagation, respectively. At high pressure, depolymerization is negligible and the rate expression has the usual form $R_p = k_p[M][P\cdot]$. Therefore, from the values of the extrapolated and experimental rates of polymerization, the equilibrium constant K ($= k_p/k_{dep}$) at ambient pressure can be directly calculated from Equation 2.4, providing a value of 0.19 $L\cdot mol^{-1}$ at 65 °C. The influence of temperature on monomer density was taken into account using data from the literature.[16]

$$K = \frac{1}{[M]\left(1-\frac{R_p'}{R_p}\right)} \qquad (2.4)$$

Using the K value reported in the literature for a polymerization at 82 °C (T_c at ambient pressure)[6], ΔH_p and ΔS_p were calculated to be -4.8 $kcal\cdot mol^{-1}$ and -18 $cal\cdot mol^{-1}\cdot K^{-1}$, respectively. The estimated value for ΔS_p is close to the usual range observed for vinyl polymerizations, whereas ΔH_p is much lower than for MMA (-13.2 $kcal\cdot mol^{-1}$).[17] A similar trend can be observed in the polymerization of α-methylstyrene (ΔH_p = -8.4 $kcal\cdot mol^{-1}$)[17] vs. styrene (ΔH_p = -16.7 $kcal\cdot mol^{-1}$)[17]. These values suggest that the kinetic data recently reported in the literature for the propagation rate coefficient of MEA at 60 °C (8.6 $L\cdot mol^{-1}\cdot s^{-1}$)[18] should be slightly corrected in order to take depropagation into account. An extrapolation to 60 °C of the above data provides a value

of 0.21 for the equilibrium constant. If this number is right, the actual value for k_p should be 13.7 $L \cdot mol^{-1} \cdot s^{-1}$.

Quantitative Correlation of Steric Effects to Polymerizability. The overall polymerization rate coefficients ($k_{pol} = k_p/k_t^{1/2}$) at 1 atm were calculated by extrapolating to atmospheric pressure and using a value of 1.41×10^{-5} for $k_d f$ (AIBN, 65 °C, 1 atm).[19] The obtained values are provided in Table 2.2. As discussed above, extrapolated coefficients obtained by this methodology correspond to hypothetical experiments where depropagation would not compete with propagation despite the fact that the polymerization is carried out below the ceiling temperature of the monomer. These depropagation-free values can be directly used to compare the relative kinetic polymerizabilities of the α-substituted acrylates.

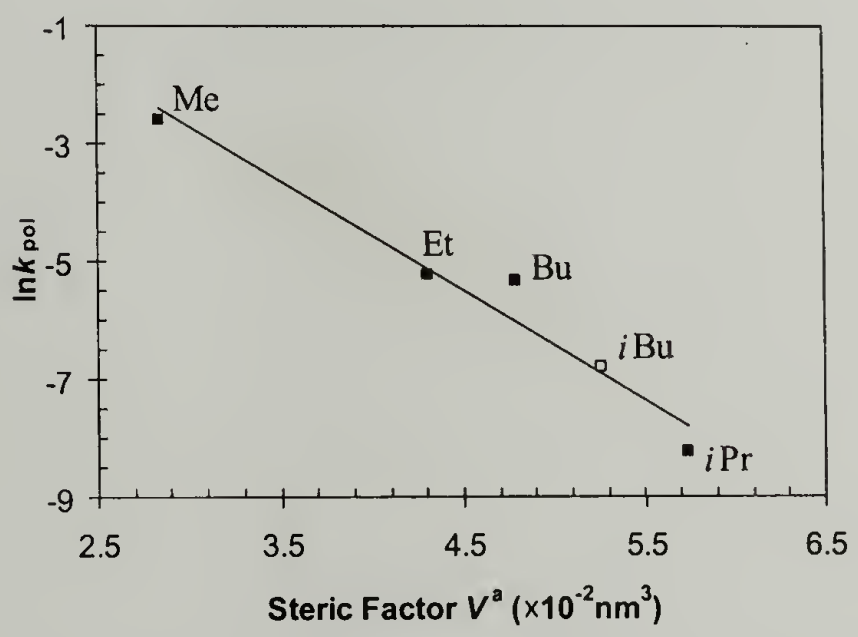


Figure 2.2. Dependence of the overall rate coefficients of polymerization for methyl α-alkylacrylates on the steric factor of the α-substituent (65 °C, 1 atm).

An attempt to correlate these polymerizability coefficients to a series of steric parameters revealed that a scale based on the steric parameters V^a proposed by Meyer[10] provided the best fit, both quantitatively (Figure 2.2) and qualitatively. The V^a values for

the alkyl groups investigated in this study are included in Table 2.2. They were obtained from the literature.[10] Such values derive from simple volume estimates based on molecular mechanics calculations and amount to the total volume occupied by the substituents in a range within 0.3 nm of the reaction center. A linear regression between polymerization coefficients and steric parameters of α-substituents based on the four data points available for MMA, MEA, M*n*BA and M*i*PA led to the following equation:

$$\ln k_{pol} = 2.86\text{-}1.86V^a \qquad (2.5)$$

Although data point obtained for M*i*BA was not used in the regression analysis because its different polymerization mechanism, it is interesting to note that the order of reactivity also correlates with the obtained results. Compared to traditional steric scales, the V^a scale also better predicts the large difference in reactivity observed between methyl and ethyl groups and the small difference observed between ethyl and butyl groups.

Although the good correlation obtained between experimental results and V^a steric parameters suggests that this scale better accounts for the steric influence exerted on the free-radical polymerizability by α-substituents, great care should be exercised in its use for substituents bearing polar groups, where other non-steric interactions will take place.

Conclusions

High pressure can be used to polymerize sterically hindered α-alkylacrylates and obtain medium-to-high molecular weight polymers from monomers that will yield only low oligomers under classical free-radical polymerization conditions. Results obtained during this study suggest that limitations to this approach might be arising not only from the sterically hindered propagation, but also from the accelerating effect of pressure on non-diffusion-controlled termination. The same approach explains why activation

volumes for polymerization of acrylates with highly sterically demanding α-substituents can be lower than for those with less bulky substituents. This work also exemplifies how extrapolation from high pressure measurement can provide kinetic data for hypothetical polymerization at ambient pressure in the absence of depropagation for low T_c monomers. These depropagation-free kinetic parameters can be used to separate thermodynamic from kinetic effects.

Meyer's steric scale was found to best describe the influence arising from the size of the α-substituent to the overall polymerizability. A linear correlation was found between V^a parameters for the substituent and the natural logarithm of the overall rate coefficient of polymerization.

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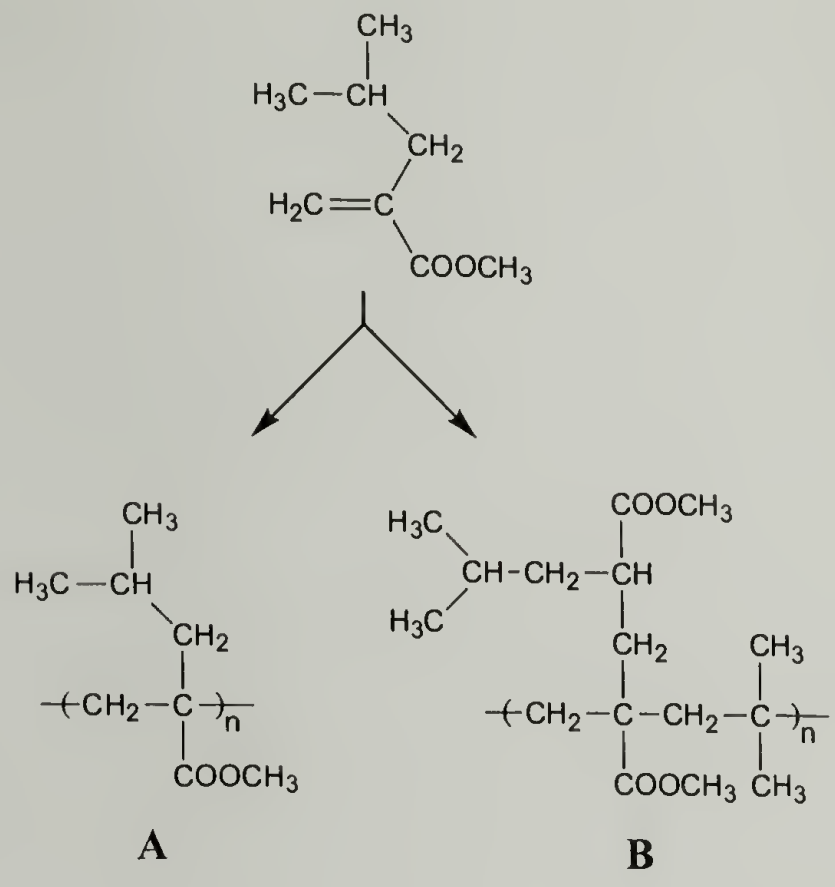
CHAPTER 3

ALTERNATING FREE-RADICAL ISOMERIZATION POLYMERIZATION OF METHYL α-ISOBUTYLACRYLATE

Introduction

In the previous chapter we described the synthesis of poly(methyl α-alkylacrylates) containing alkyl pendant groups of variable size and branching. The well-known difficulty in polymerizing α-alkylacrylate monomers when the alkyl substituent is larger than a methyl (MMA) was overcome by using high pressures as both a kinetic and thermodynamic additional driving force for the free-radical polymerization. This methodology allowed us to obtain for the first time acrylic polymers that are thermodynamically unstable at room temperature and pressure (ceiling temperature T_c < 25 °C) and whose metastability could be used to generate lithographic pattern by controlled degradation in the presence of external triggers (heat, UV light, e-beam). An ongoing investigation of the structure-degradability relationships in this series of polymers indicated a very peculiar behavior for one of the polymers, poly(methyl α-isobutylacrylate), that could not be rationalized easily and forced us to reconsider its assigned structure **A** (Scheme 3.1). In this chapter, we will present a full NMR re-investigation of the polymer and describe a previously unreported, efficient intramolecular rearrangement of the acrylic propagating free-radicals whose thermodynamic driving force largely derives from the need to minimize steric strain in these highly crowded polymers.

Scheme 3.1 Polymerization of methyl α-isobutylacrylate.



Experimental Section

Synthesis of the monomer, methyl α-isobutylacrylate (M*i*BA), and its high-pressure free-radical polymerization were conducted as described in Chapter 2. A typical example is as follows: 1.43 g of M*i*BA (1.0×10^{-2} moles) carefully deoxygenated with nitrogen for 20 min and 0.011g of 2,2'-azobis(isobutyronitrile) (6.7×10^{-5} moles) were mixed and transferred under a nitrogen atmosphere to a 1.3 mL Teflon reaction vessel until the container was fully loaded. The ampule was hermetically closed and weighed to calculate the exact amount of monomer and initiator. The polymerization was run at 5 kbar and 65 °C for 6 hours, using a high-pressure reactor designed by the High-Pressure Research Center of the Polish Academy of Science. Precipitation in hexanes yielded 0.102 g of a white powder (13.4 %), with the following molecular weight characteristics as determined by SEC (THF, poly(methyl methacrylate) calibration): $M_n = 40 \times 10^3$,

$M_w/M_n = 1.61$). Thermogravimetric analysis (DuPont TA 2050, 10 °C·min^{-1}, nitrogen) of the obtained poly(methyl α-isobutylacrylate) showed that no decomposition leading to volatile products took place below 190 °C.

NMR spectra were recorded at 150 °C in d_5-nitrobenzene using a Bruker Avance 600 spectrometer operating at 600.03 MHz (^{1}H) and 150.88 MHz (^{13}C). For ^{1}H NMR analysis, samples with a concentration of 10 mg·mL^{-1} were used and chemical shifts were referenced to the most upfield solvent resonance of nitrobenzene at 7.50 ppm. ^{13}C NMR spectra were recorded under proton decoupling at a concentration of 100 mg·mL^{-1} and the most upfield peak of the solvent resonance at 123.5 ppm. Conditions for the ^{13}C NMR experiments were not optimized to allow quantitative analysis. A DEPT technique was used to determine multiplicity of the peaks in the ^{13}C spectra. 2D NMR experiments, phase sensitive ^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOR, were used to establish couplings between corresponding nuclei. Proton-carbon correlation was performed with direct carbon observation because of the absence of a gradient probe that would take the requisite high temperature. The delay before the final 90 degree antiphase refocusing pulses was 3.45 ms followed by a 2.29 ms delay to capture intensity from all carbon multiplicities. Forty two 32-scan, 4k slices were obtained with 0.3 s acquisition time and 2 second recycle delay. TPPI phase sensitive proton-proton COSY spectra were obtained from 128 4-scan 2k slices with an 0.426 s acquisition time and 1 second recycle delay.

Results and Discussion

High-pressure (5-8 kbar) free-radical polymerizations of methyl α-isobutylacrylate initiated by 2,2'-azobisisobutyronitrile at 65 °C resulted in a white, powdery polymer soluble in most common organic solvents. NMR analysis of the polymer was conducted

at 150 °C in d_5-nitorbenzene. The proton decoupled ^{13}C NMR spectrum of the polymer is provided in Figure 3.1. Degree of substitution for each carbon (C, CH, CH_2, CH_3) was determined by DEPT as shown in Figure 3.2. The ^{1}H NMR spectrum of the polymer is presented in Figure 3.3, with the proton peaks unambiguously assigned by a ^{1}H-^{13}C HETCOR experiment (Figure 3.4a). Finally, couplings between protons were determined by a ^{1}H-^{1}H COSY experiment (Figure 3.4b), the results of which are also summarized in Figure 3.3.

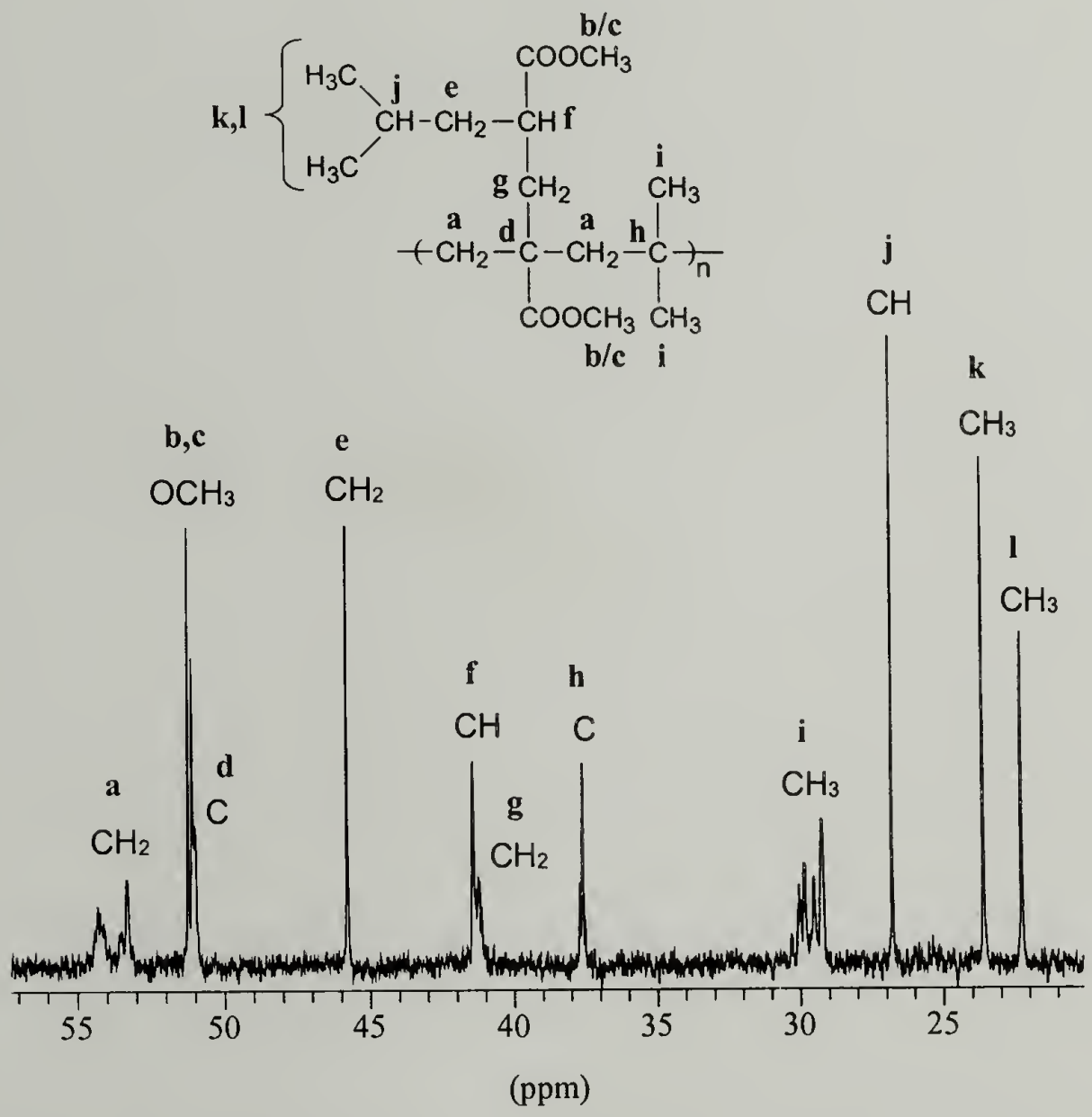


Figure 3.1. ^{13}C NMR spectrum of poly(M*i*BA) (150 °C, d_5-nitrobenzene).

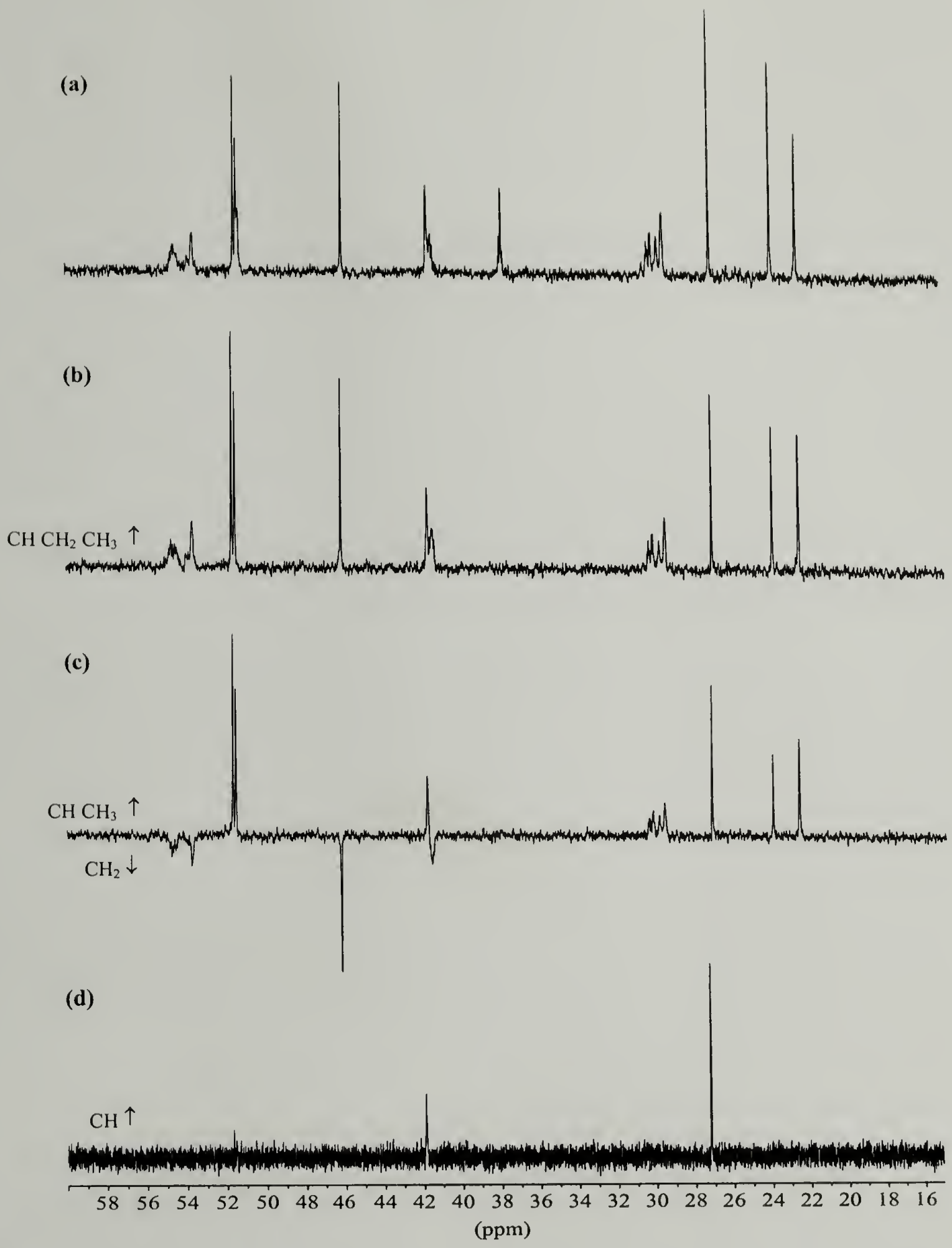


Figure 3.2. DEPT analysis of poly(MiBA): (a) ^{13}C NMR, (b) DEPT 45, (c) DEPT 135, (d) DEPT 90.

Assuming that the polymerization proceeds through a vinyl double bond addition in a traditional way, structure **A** should be obtained for the polymer. In the ^{13}C NMR spectrum, peaks expected for structure **A** are observed (methyl groups **k** and **l**, methine group **j** from the isobutyl side group) together with another set of peaks shifted downfield, suggesting the existence of an isomeric structure. Particularly noticeable are two tertiary (**f** and **j**) carbons separated by more than 10 ppm. The observed difference in chemical shifts for the two sets of peaks cannot be explained simply by the presence of stereoisomeric units as tacticity usually leads to small variation in chemical shifts, typically within a few ppm range. Likewise, in the ^{1}H NMR spectrum, two methine protons separated by more than 1 ppm can be observed, with one of the peaks showing up above 3 ppm, a highly unusual chemical shift for a simple aliphatic CH.

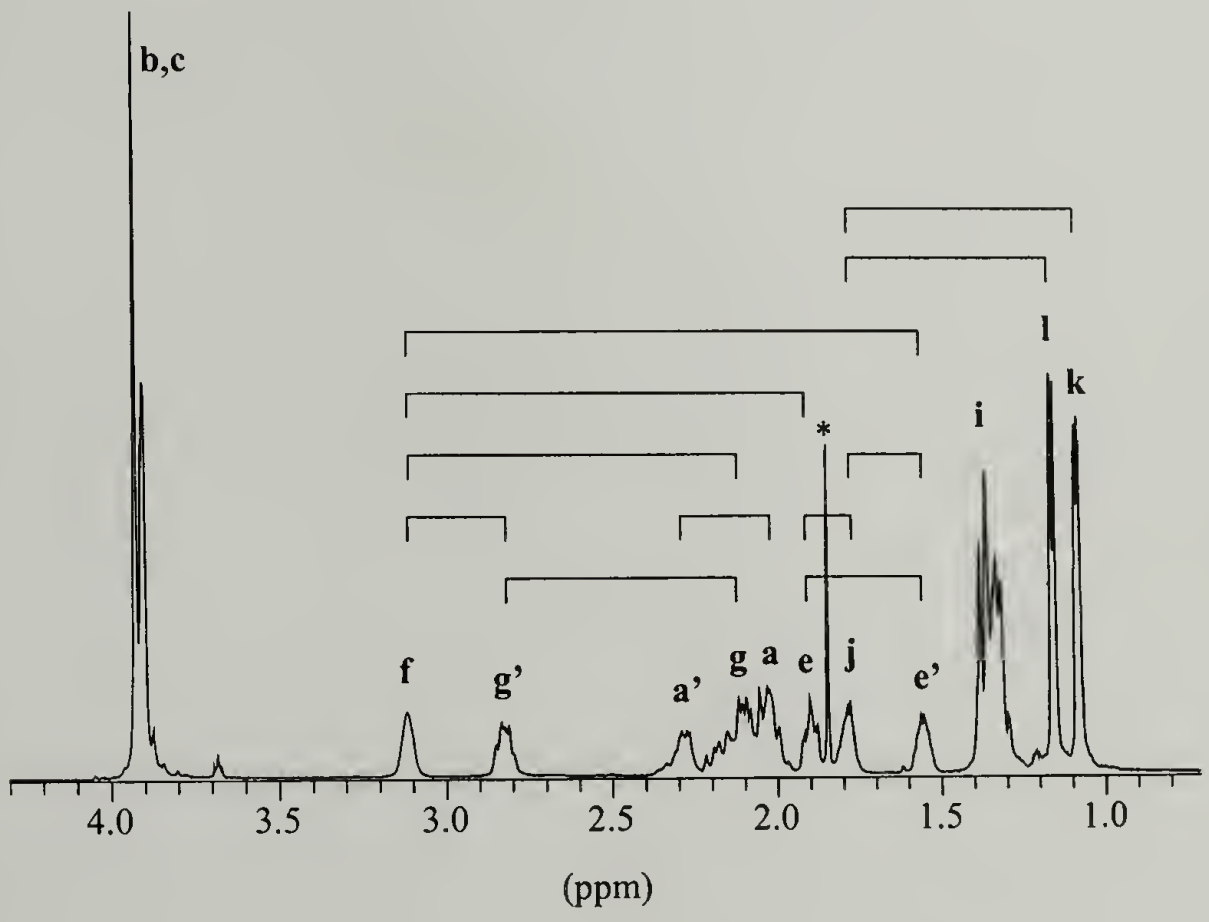


Figure 3.3. ^{1}H NMR spectrum of poly(M*i*BA). Brackets indicate the couplings between protons as determined by a ^{1}H-^{1}H COSY experiment.

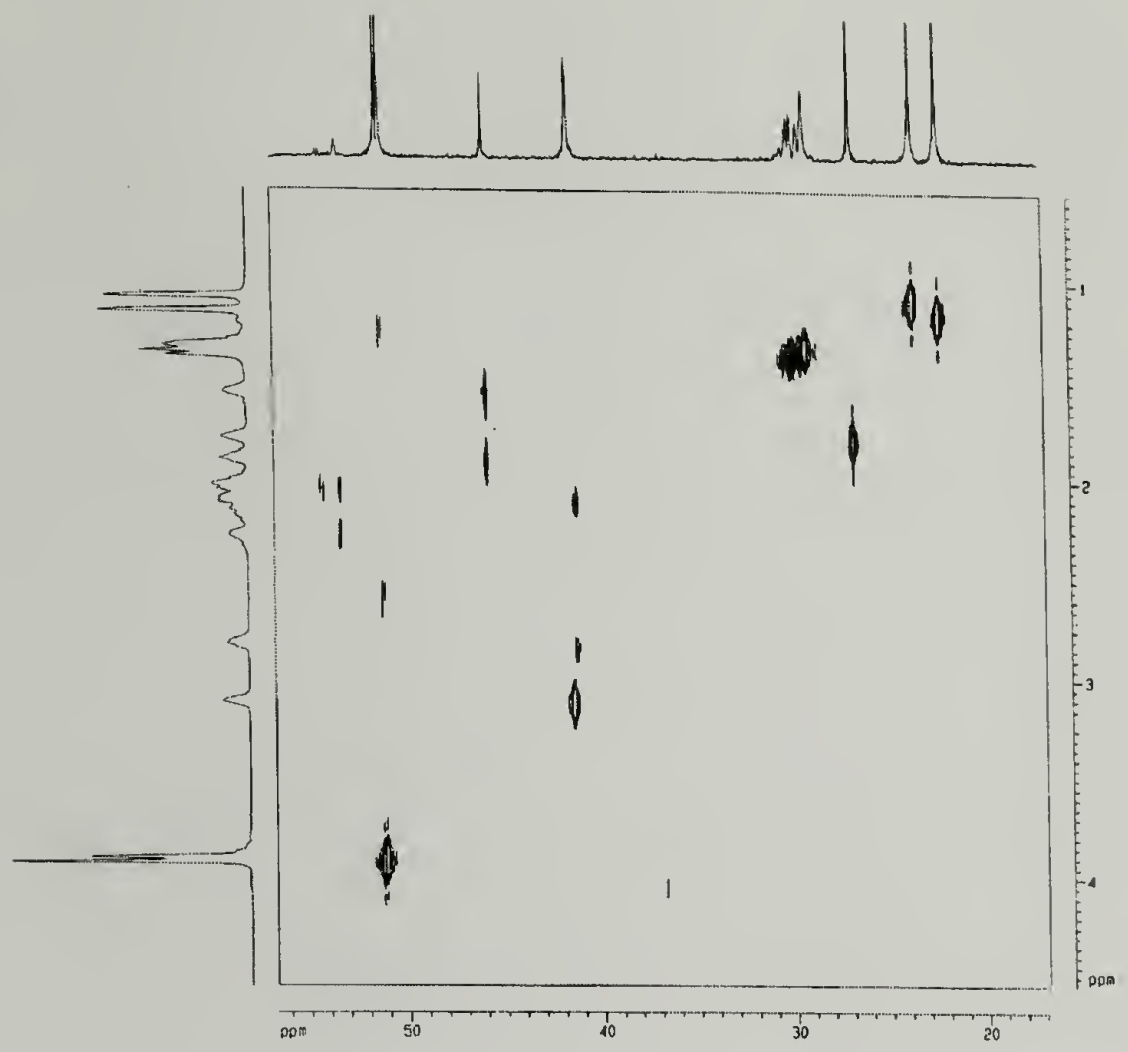
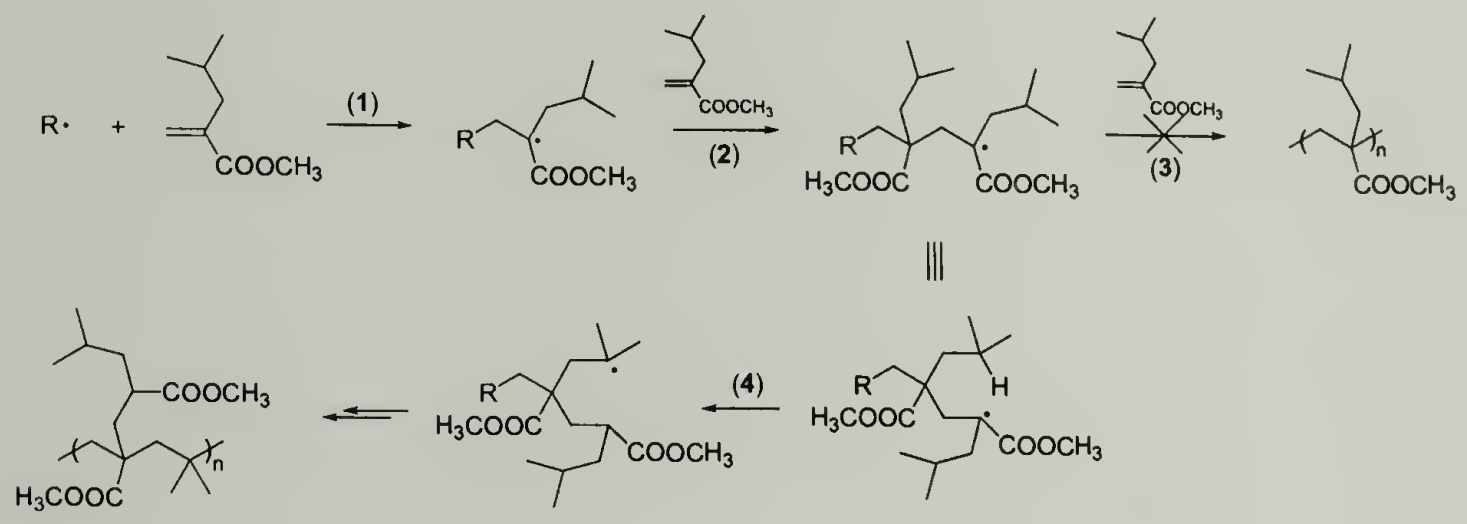


Figure 3.4. ^{1}H-^{13}C HETCOR (a) and ^{1}H-^{1}H COSY (b) spectra of poly(M*i*BA).

Clear evidence that structure **A** is wrong arises from the ^{1}H-^{1}H COSY experiment (Figure 3.4b), the results of which are also summarized in Figure 3.3. The two most striking features are: (a) one of the methyl groups **i** is not coupled to any of the CH's, and (b) one of the CH protons **f** is coupled to the protons of two different CH_2 groups. In order to account for this spectroscopic evidence, structure **B** has to be assumed for the polymer. This isomeric structure can be obtained as a result of an intramolecular hydrogen transfer process during propagation (Scheme 3.2). Assignment of carbons for structure **B** is shown in Figure 3.1. Methyl groups **l** and **k** are part of the isobutyl side group, and are in slightly different electronic environments probably due to some hindered rotation around the C_j-C_e bond. Methyl groups **i** are directly attached to the backbone, and their ^{1}H and ^{13}C NMR signals show multiple splittings, which can be attributed to a stereoisomeric effect (tacticity with respect to the substituents on the carbon **d**). In the proposed structure **B**, methyl protons **i** cannot be coupled to any other proton as they are attached to a quaternary carbon. The methine proton **j** of the isobutyl side-group is coupled to protons of both methyl groups **l** and **k** (J = 6.3 Hz), as well as to the methylene protons **e**, as expected. The methine group **f**, which is formed during the intramolecular 1,5 hydrogen shift, is similar to the CH groups of a polyacrylate backbone. In agreement with this fact, its ^{1}H (3.1 ppm) and ^{13}C (41.5 ppm) chemical shifts are very close to the values observed for polyacrylate methine groups (2.4-2.8 and 41-42 ppm for ^{1}H and ^{13}C, respectively).[1] Protons **f** are coupled to protons of two methylene groups **g** and **e**, a feature impossible to rationalize in terms of structure **A**. By integrating the ^{1}H NMR spectrum, it was possible to obtain the relative amounts of each proton in the polymer structure. From the 1:1 ratio of signals for protons **f** and **j**, and 1:6 ratio for

protons **f** and **b**+**c**, it is possible to conclude that structure **B** effectively describes the polymer, with no structure **A** present as a comonomer unit.

Scheme 3.2 Proposed mechanism for the polymerization of M*i*BA.



Intramolecular 1,5 hydrogen shifts are facilitated by the formation of a six-membered ring transition state and have been widely observed for small free-radicals.[2] A few examples of such shifts are also known in polymer chemistry, the most common example being the free-radical polymerization of ethylene to branched low-density polyethylene.[3] Intramolecular hydrogen shifts in this backbiting mode have also been reported to occur to some extent during the free-radical polymerizations of acrylates.[4-6] The rearrangement reported here is unique in the fact that the alkyl radical resulting from the rearrangement is thermodynamically less stable than the initial ester group-stabilized, propagating free-radical. It seems reasonable to assume that in this case the thermodynamic driving force arises in part from the release of the steric strain in the polymer that results from the intramolecular hydrogen shift.

Another noteworthy feature of this rearrangement results from the fact that the 1,5-hydrogen shift (step 4 in Scheme 3.2) occurs much faster than the propagation (step 3).

As a result, a clean alternating structure **B** is obtained, with side-to-side insertion of two two-carbon units: an isobutylene and a complex, α-branched methyl acrylate.

A few isomerization polymerizations have been described in the literature where the propagating species rearrange rapidly by either a ring-opening, or a proton or hydride shift, before addition of the resulting species to another monomer molecule occurs.[7-9] To the best of our knowledge, all of these isomerizations involve atoms that are part of the last added unit. In the case investigated here, isomerization requires the subsequent addition of two units, the rearrangement taking place only after the second unit has been added and involving a hydrogen shift from the first to the second unit.

The unexpected rearrangement described in this note provides another striking example of the difficulty associated with the polymerization of olefins 1,1-disubstituted by large substituents. The steric strain associated with the presence of bulky substituents on every second carbon alongside the backbone makes polymerization of these monomers very difficult. The use of high pressures allows to partly circumvent the problem, but it must be realized that under these more extreme conditions, reactions unreported under "normal" conditions can appear, entirely modifying the expected course of the polymerization.

Conclusions

Polymers obtained by high-pressure free-radical polymerization of methyl α-isobutylacrylate were extensively characterized by 1D and 2D NMR. Based on the spectroscopic evidence, it was demonstrated that the polymer had an unusual isomeric structure of alternating isobutylene and α-branched acrylate units. A polymerization mechanism was proposed to account for this polymer structure, involving a 1,5-hydrogen

shift from the isobutyl side group of the penultimate unit to the acrylic propagating species.

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CHAPTER 4

INFLUENCE OF THE α-SUBSTITUENT ON THERMAL PROPERTIES AND DEGRADATION BEHAVIOR OF POLY(METHYL α-ALKYLACRYLATES)

Introduction

In Chapter 2, we suggested the use of very high hydrostatic pressure (1-10 kbar; 1 kbar = 10^5 Pa ≈ 1,000 atm) as a kinetic and thermodynamic driving force to achieve polymerization of bulky α-substituted acrylates. Hydrostatic pressure favorably shifts the propagation-depropagation equilibrium during the polymerization, and as a result increases the ceiling temperature T_c. Pressure has also a positive kinetic influence on chain polymerizations by speeding up propagation and slowing down diffusion-controlled terminations via an increase in viscosity.[1,2] We demonstrated that by using high pressure high molecular weight polymers can be obtained for various methyl α-alkylacrylates with alkyl groups ranging from ethyl to isobutyl.

It can be reasonably assumed that the strong steric interactions that make the polymerization of these monomers so difficult will also facilitate their depolymerization. Some of the polymers obtained in our previous studies have extrapolated ceiling temperatures at ambient pressure well below room temperature, i.e. are thermodynamically unstable at ambient pressure and temperature, and as such should spontaneously degrade back to the monomer under those conditions. This does not happen, however, because no kinetic pathway for the depolymerization is available. Polymers existing in such a metastable state are very susceptible to degradation when an initiation mechanism is provided generating the required macromolecular free radicals.

This can be achieved by using external triggers such as heat, UV light or redox catalysts to homolytically cleave the labile bonds (whose properties and placement can be tuned) in the polymer backbone and initiate depolymerization.

In this Chapter, we investigate the structure-property relationships for the metastable poly(methyl α-alkylacrylates), with an emphasis on their degradation behavior in the presence of external triggers such as heat or UV light.

Experimental Section

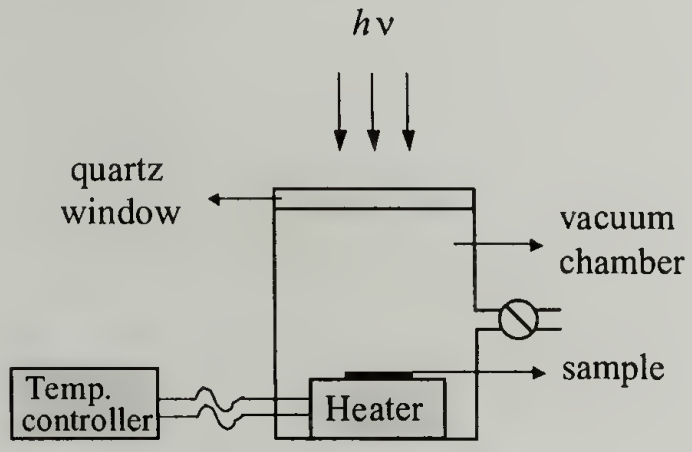
Samples. The synthesis of methyl α-alkylacrylates and their polymerization under high-pressure conditions has been described in Chapter 2.

Measurements. The molecular weights of the polymers were determined by GPC using a Waters 510 HPLC pump, a Waters R400 differential refractometer detector, and a three-column set (PLgel, 5 μm, 1x 50 Å and 2x MIXED-D). Measurements were conducted at 1.0 $mL.min^{-1}$ in tetrahydrofuran, and the system was calibrated with polystyrene standards. ^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz Bruker Avance spectrometer at 150 °C in d_5-nitrobenzene. Glass transition temperatures (T_g) of the polymers were measured by DSC using a DuPont 2910 at a heating rate of 10 $^{o}C{\cdot}min^{-1}$ under nitrogen. The thermal stability of the polymers was investigated by TGA on a DuPont TA 2050 under nitrogen at a heating rate of 10 $^{o}C{\cdot}min^{-1}$. Thermal decomposition products were analyzed on a HP 5890 Series II gas chromatograph coupled to a HP 5972 mass spectrometer. Film thicknesses were measured by ellipsometry using a Rudolph Research AutoEl-II ellipsometer (70° incident angle, helium-neon laser).

Photodegradation Studies. Photodegradation experiments were conducted in a

home-built apparatus, consisting of a vacuum chamber with a quartz window, and a heating plate attached to a temperature controller (Scheme 4.1). Thin films of polymers (300-400 nm) were obtained by spin coating from toluene solutions onto silicon wafers (International Wafer Service). Samples of about 1 cm^2 were placed under dynamic vacuum ($1\text{-}3\times10^{-2}$ mmHg) inside the chamber, heated to a targeted temperature and irradiated with a low-pressure mercury lamp (UVP XX-15S, 15W) located at 5 cm from the sample. The UV lamp had a strong emission band at 254 nm, whose intensity as measured by a UVP UVX Radiometer with a UVX-25 sensor was 24 $mW{\cdot}cm^{-2}$ at the location of the sample. Samples were taken out at certain time intervals, and their thicknesses measured.

Scheme 4.1 Experimental setup for the photodegradation studies.

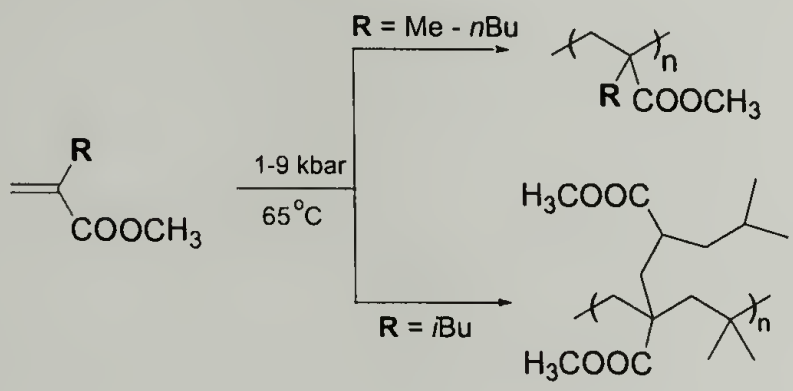


Results and Discussion

Polymer Synthesis. The poly(methyl α-alkylacrylate)s investigated in this study were synthesized using experimental procedures described in Chapter 2. Experimental conditions used for the synthesis, and the molecular weights of the obtained polymers are summarized in Table 4.1. While acrylates with linear alkyl α-substituents polymerized via C=C bond addition as usual, polymerization of methyl α-isobutylacrylate proceeded in alternating steps of monomer addition and intramolecular 1,5 hydrogen shift from the

isobutyl group of a penultimate unit, providing an unusual isomeric structure depicted in Scheme 4.2 (see Chapter 3).

Scheme 4.2 Polymerization of methyl α-alkylacrylates.



Acrylate	R
MMA	-CH_3
MEA	-CH_2CH_3
M*n*PA	-$CH_2CH_2CH_3$
M*i*PA	-$CH(CH_3)_2$
M*n*BA	-$CH_2(CH_2)_2CH_3$
M*i*BA	-$CH_2CH(CH_3)_2$

Table 4.1. Polymerization conditions and molecular weight characteristics of the poly(methyl α-alkylacrylates) used in this study.[a]

Monomer	*P* (kbar)	M_n[b] ($\times 10^{-3}$)	$\frac{M_w}{M_n}$ [b]
MEA	0.001	1.8	1.60
	1	6.2	1.40
	3	22	1.75
	5	69	2.22
	6	120	2.27
	9	139	3.61
M*n*PA	5	149	2.37
M*i*PA	9	8.4	1.28
M*n*BA	5	138	2.90
M*i*BA	5	40	1.61

[a] Polymerizations conducted at 65 °C.
[b] Obtained by GPC relative to polystyrene standards.

Influence of Pressure and Monomer Structure on the Tacticity. The tacticity of vinyl polymers is known to affect their physical properties. As a result, tacticities of the synthesized poly(methyl α-alkylacrylate)s were measured by ^{1}H NMR at 150 °C in d_5-nitrobenzene. Previous studies based on oligomers obtained by anionic polymerization

had indicated that the methyl ester signal for poly(MEA) splits into three peaks corresponding to the three possible triads (*rr*, *mr*, *mm*).[3,4] Backbone methylene protons could not be used to determine tacticities at the dyad and tetrad levels due to an overlap between backbone and side-chain methylene proton signals.

Figure 4.1 shows the observed methyl ester peak of poly(MEA) and the corresponding assignments for the triads. Similar assignments were tentatively used for the determination of triad-level tacticities for the other poly(methyl α-alkylacrylates). As the influence of an alkyl group on the local environment of methyl ester protons and the corresponding chemical shifts is minimal and is not affected very much by the nature of the alkyl group, such an assumption appears reasonable. In the case of poly(M*i*PA) tacticity analysis was prohibited by the broadness of the peaks and poor resolution of the ^{1}H NMR spectrum.

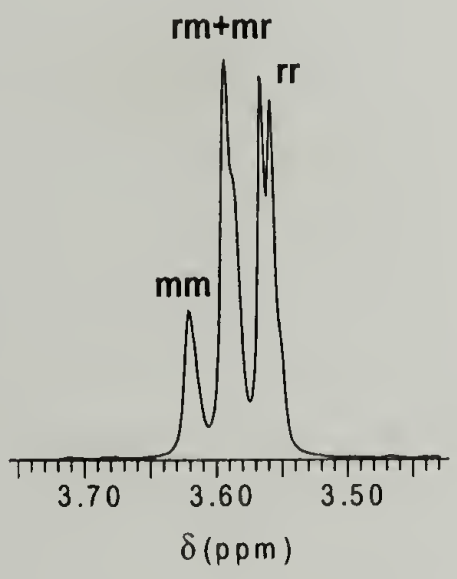


Figure 4.1. Methyl ester region of the ^{1}H NMR spectrum of poly(MEA) (150 °C, d_5-nitrobenzene).

For the methyl α-alkylacrylates investigated in this study, pressure was found to have almost no effect on the stereoregularity of the polymerization. Results shown in Figure 4.2 clearly indicate that the tacticity of poly(MEA) remains constant within experimental

error for polymerization conditions ranging from 1 to 9 kbar. Pressure also did not have noticeable effect on the stereochemistry of M*n*BA polymerizations.

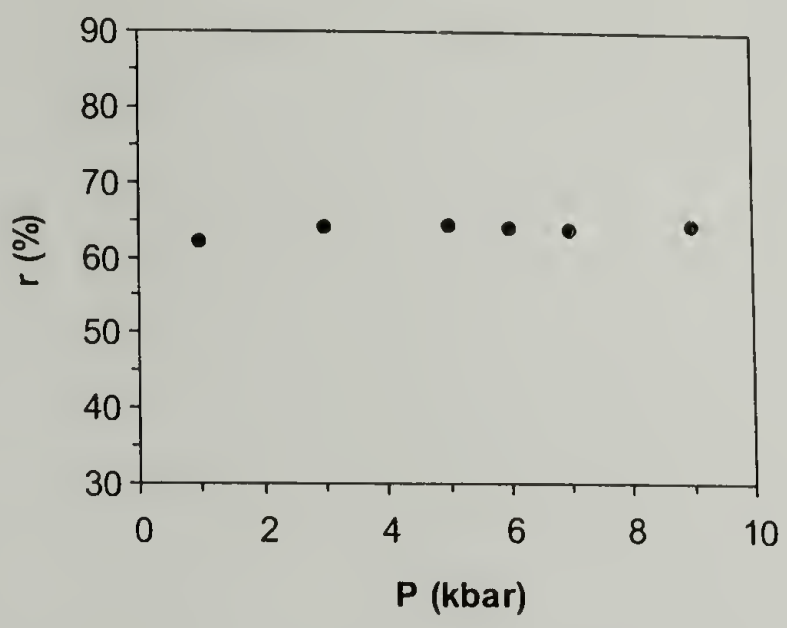


Figure 4.2. Dependence of the amount of racemic dyads in poly(MEA) on the polymerization pressure.

Influence of pressure on the stereochemistry of a free-radical polymerization has been studied only for a limited number of monomers. For the polymerization of MMA[5] and vinyl chloride,[6] pressure was found to increase the number of isotactic units in the polymer. For example, in the case of MMA polymerization, higher pressure led to a small decrease in the syndiotacticity of the polymer from 75% at 0.001 kbar (1 atm) to 62% at 8 kbar.[5] On the other hand, poly(isopropenyl acetate) samples obtained by free-radical polymerization at 0.001 and 5 kbar had the same stereoregularities.[7] It seems reasonable to speculate that, steric and electronic effects of the alkyl and ester group internally compensate in such a way that activation volumes for isotactic and syndiotactic additions become equal, and pressure has no net effect on the stereochemistry of MEA polymerization.

Table 4.2. Stereochemical characteristics of poly(methyl α-alkylacrylates).[a]

Substituent **R**	*r* (%)	*mm* (%)	*mr* (%)	*rr* (%)	$p_{m/r}$	$p_{r/m}$	*S*
Methyl[b]	73	8	38	54	0.70	0.26	0.96
Ethyl	64	12	48	40	0.67	0.37	1.04
n-Propyl	61	17	44	39	0.57	0.36	0.93
n-Butyl	66	15	38	47	0.56	0.29	0.85

[a] Polymers synthesized at 65 °C and 5 kbar.
[b] Ref. 14 (synthesized at 51 °C and 4.7 kbar).

Tacticity values for poly(methyl α-alkylacrylate)s synthesized at 5 kbar are provided in Table 4.2. Increase in the size of the α-substituent decreases stereoregularity of the polymerization and leads to less syndiotactic polymers. While an initial shift from a methyl to an ethyl group on the α-position has a noticeable effect on the tacticity, further increase in the length of the α-alkyl substituent has almost no influence.

By analyzing conditional probabilities for meso and racemo additions during propagation, it is possible to obtain information on the polymerization mechanism. For a process where addition of the monomer to the polymer chain is independent of the stereochemical configuration of the chain-end, stereoregulation is governed by Bernoullian statistics and the following equation should be valid:

$$S = p_{r/m} + p_{m/r} = 1 \qquad (4.1)$$

where $p_{r/m}$ and $p_{m/r}$ are conditional probabilities of meso and racemo additions, respectively. From the *S* values provided in Table 4.2 for the investigated poly(methyl α-alkylacrylate)s, it can be concluded that the polymerizations of MEA and M*n*PA follow Bernoullian statistics as the value of *S* is close to 1 for both systems. In the case of M*n*BA, a slight deviation is observed ($S = 0.85$), which is probably related to the increased size of the α-substituent. Similar deviations have been reported for the

polymerization of other α-substituted acrylates with bulky α-substituents such as methyl α-benzylacrylate[8] and methyl α-(2,2-bis(carbomethoxy)ethyl)acrylate.[9]

Glass Transition in Poly(Methyl α-Alkylacrylates). Glass transition temperatures for poly(MEA)s synthesized at different pressures and possessing different molecular weights were plotted against number average degree of polymerization X_n obtained by GPC relative to polystyrene standards (Figure 4.3). Data were fitted using Equation 4.2, which had been shown to describe the molecular weight dependence of T_g for other well-studied polymers such as PMMA better than the traditional Flory-Fox equation.[10] Since the polymerization pressure had no effect on the tacticities of the obtained polymers, such an analysis appears reasonable. By extrapolation to infinitely high molecular weights, a T_g^{∞} value of 70 °C was found for poly(MEA).

$$T_g = T_g^{\infty} - K/X_n^{2/3} \qquad (4.2)$$

T_g values obtained for poly(MEA) (70 °C) and poly(M*n*PA) (53 °C) differ significantly from those previously reported by Cheng *et al.*, i.e. 57 and 25 °C, respectively.[11] We attribute this difference to the fact that the latter polymers were obtained by polymerizing the corresponding α-alkylacrylic acids and subsequent methylation. Therefore, they most probably have stereoregularities very different than for the polymers investigated here, which affects their glass transition temperatures. The fact that molecular weights of the polymers in this study are much higher than those obtained by Cheng *et al.* may be another source for the discrepancy. In another study, Burel *et al.* reported an even higher T_g^{∞} value of 111 °C for a poly(M*n*PA) that was obtained by methylation of poly(*n*-propylacrylic acid).[12] A careful analysis of the T_g - X_n

curve reported in this paper suggests that the extrapolating procedure adapted by the authors artificially overestimates T_g^{∞} in this case.

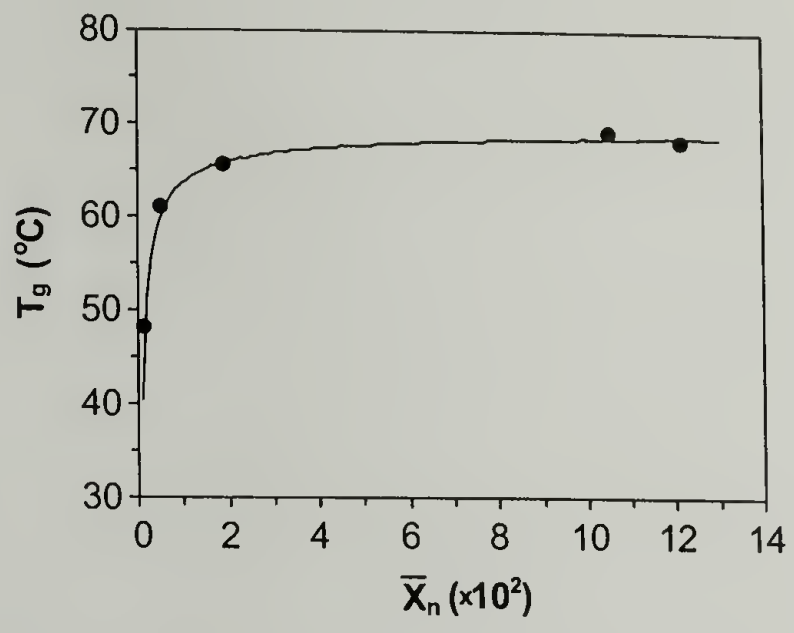


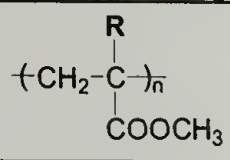
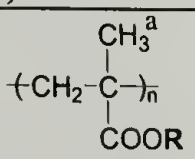
Figure 4.3. Dependence of T_g on the number average degree of polymerization of poly(MEA) (obtained by GPC relative to polystyrene standards). Solid line represents a curve fitted by using Equation 4.1.

T_g values for the entire series of poly(methyl α-alkylacrylate)s are summarized in Table 4.3 along with the literature values for the corresponding isomeric poly(alkyl methacrylate)s[13,14] with similar tacticities (r = 60-70%). The T_g value for the polymer obtained from M*i*BA polymerization was 64 °C. It corresponds to the isomeric polymer structure shown in Scheme 4.2 and therefore should not be compared to the other polymers in the series.

In both cases (poly(methyl α-alkylacrylate)s and poly(alkyl methacrylate)s), an increase in size of the *n*-alkyl substituent (Me → Et → *n*-Pr) first depresses T_g. This trend is interrupted for poly(methyl α-alkylacrylate)s when a butyl group is introduced on the α-position (T_g (*n*-Pr) = 53 °C vs. T_g (*n*-Bu) = 61 °C), while for the poly(alkyl methacrylate)s the trend continues.[13] Increasing the size of the alkyl substituent not only increases the free volume and flexibility of the side chain, which should lead to a drop in

T_g; it also increases the rigidity of the backbone as a result of stronger steric repulsions, which should have an opposite effect on T_g. For poly(methyl α-alkylacrylate)s, the second factor appears to prevail at the transition from a propyl to a butyl group. Larger and bulkier groups such as an *iso*-propyl increase the rigidity of the backbone even further, and therefore result in higher T_gs.

Table 4.3. Glass transition temperatures of poly(methyl α-alkylacrylates) and corresponding poly(alkyl methacrylates).

Substituent **R**	T_g (°C)	
		
Methyl	104	104
Ethyl	70	66
n-Propyl	53	35
iso-Propyl	121	81
n-Butyl	61	19

[a] From Ref. 13,14.

Relative to poly(alkyl methacrylate)s with the same alkyl group, poly(methyl α-alkylacrylate)s have higher T_gs as a result of the α-substituents being much closer to the backbone and therefore having a stronger influence on the backbone flexibility than when the substituent is on the ester position. Poly(M*i*PA) has the highest T_g at 121 °C, indicating high stiffness and restricted mobility of the backbone as a result of repulsive interactions between sterically demanding isopropyl α-substituents. The highly rigid nature of this polymer is further supported by the ^{1}H NMR spectrum where, even at 150 °C, only broad and unresolved peaks can be observed.

Thermal Stability of Poly(Methyl α-Alkylacrylates). Thermogravimetric curves for the poly(methyl α-alkylacrylate)s series are shown in Figure 4.4. All polymers

showed complete degradation with a zero char yield. Unlike PMMA, which has been shown to degrade by a multi-step depolymerization process,[15] all our polymers - except one - showed a single-step decomposition behavior. The only exception was poly(M*i*BA) whose degradation started below 200 °C and proceeded in two steps. This behavior can be attributed to the complex α-branched structure of poly(M*i*BA) (see Scheme 4.2).

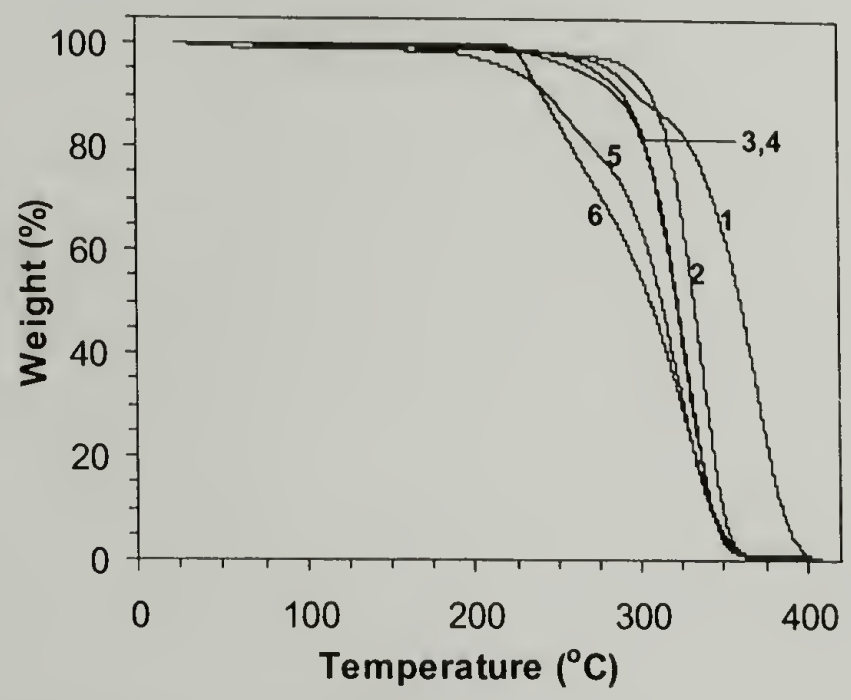


Figure 4.4. Thermogravimetric curves of poly(methyl α-alkylacrylates): (1) PMMA, (2) poly(MEA), (3) poly(M*n*PA), (4) poly(M*n*BA), (5) poly(M*i*BA), (6) poly(M*i*PA). TGA conditions: 10 °C·min^{-1}, under N_2.

Thermal decomposition products of poly(MEA) were characterized by GC-MS. Solid poly(MEA) depolymerized mostly to its monomer, with some residual dimer and trimer formation. This behavior is similar to the well-studied degradation of PMMA, which also decomposes mainly to its monomer. Thermal depolymerization of some poly(MEA) samples could also be observed in solution. While poly(MEA) samples obtained at 1 kbar and above were stable at 150 °C, a polymer synthesized at atmospheric pressure partly decomposed to its monomer when heated at 150 °C in d_5-nitrobenzene. Peaks attributable to MEA could be observed in ^{1}H NMR after just a few minutes of

heating (Figure 4.5). The TGA of this sample showed a multi-step degradation pattern with the first decomposition starting around 150 °C. A similar behavior has been observed for PMMA, with the weight loss below 200 °C usually attributed to a depolymerization initiated by the cleavage of weak head-to-head linkages formed during termination by recombination.[16] The difference in thermal behavior between poly(MEA)s synthesized at atmospheric and high pressures could arise from the fact that the former sample has a very low molecular weight (~ 1.8×10^3), and therefore a high concentration of chain-ends.

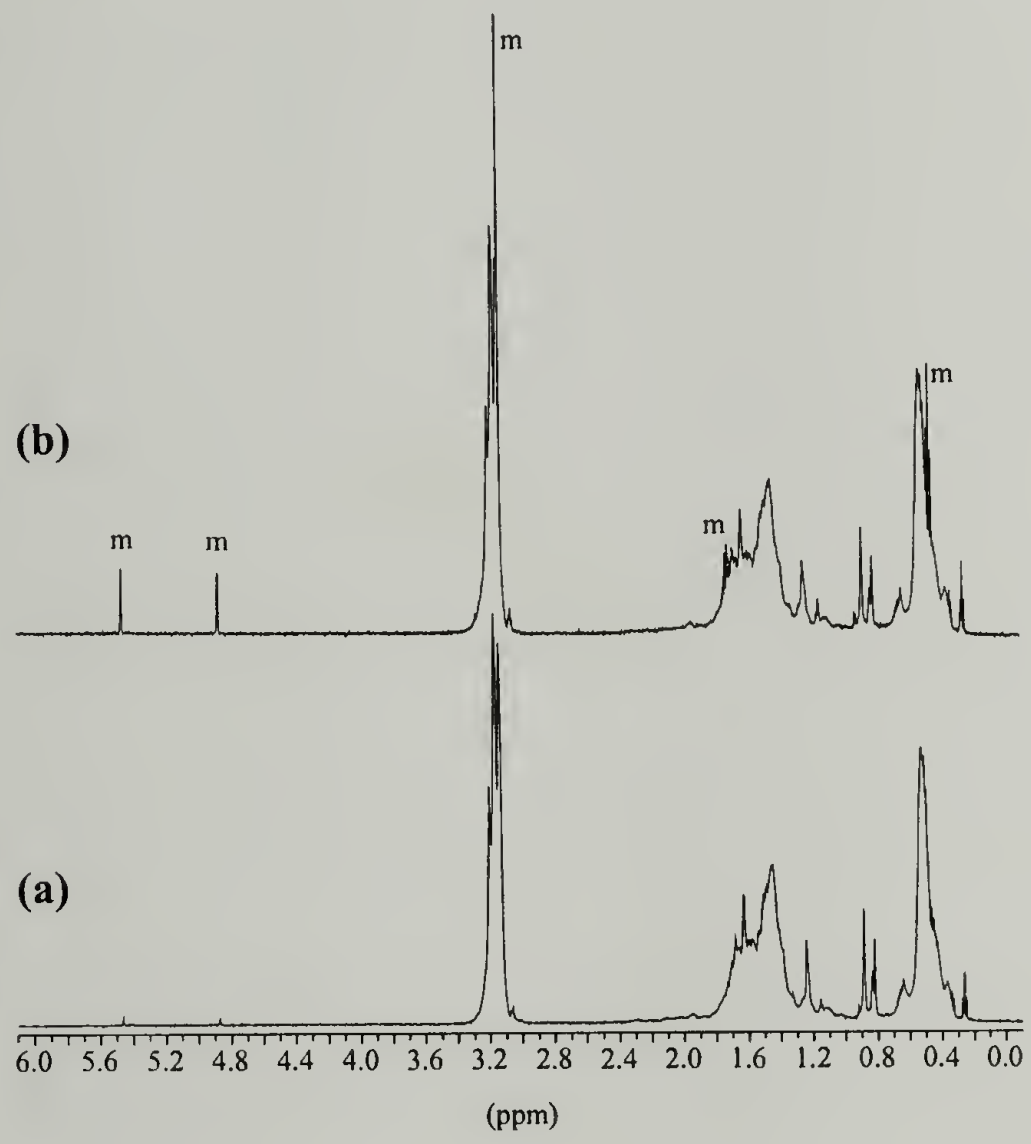


Figure 4.5. ^{1}H NMR spectra of poly(MEA) at 150 °C after 0 (a) and 5 (b) min. Signals corresponding to the forming monomer MEA are marked as *m*.

Thermal degradation of poly(MiBA) resulted in the formation of three major volatile fractions separated and identified by GC-MS: isobutylene (surface area of 27 % in the

chromatogram), M*i*BA (17 %), and a higher molecular weight fraction containing an acrylic dimer (49 %). The relative amounts of degradation products were obtained by comparing the corresponding peak areas in the GC chromatogram, and therefore do not correspond to the true molar ratios. Formation of products similar in structure to the repeating units of the polymer suggests that the degradation involves an unzipping process. Release of M*i*BA during the decomposition process probably is a result of rearrangement events similar to those occurring during the polymerization (see Chapter 3). A significant number of minor products were also formed, suggesting a more complicated degradation process.

As expected, thermal stabilities of the polymers decreased with increasing size of the α-substituent in the order: PMMA > poly(MEA) > poly(M*n*PA) ≈ poly(M*n*BA) > poly(M*i*BA) > poly(M*i*PA). The large steric hindrance associated with the α-substituents, which makes the formation of these polymers difficult, results in thermodynamically metastable structures of increasing instability.

Photodegradation of Poly(Methyl α-Alkylacrylates). The photodegradability of poly(MEA) under 254 nm UV irradiation was studied at 100 °C using experimental setup described in Scheme 4.1, and was compared to that of PMMA. The photodegradation of both polymers was monitored by measuring the decrease in film thickness. Volatile products were evacuated under dynamic vacuum. As shown in Figure 4.6, poly(MEA) almost quantitatively degraded to volatile products in five hours, while the film thickness of PMMA remained mostly unchanged during this time. According to the literature, the mechanism of photodegradation for PMMA involves a cleavage of an ester side-group, providing a radical on the main chain, and a subsequent depolymerization (Scheme 4.3,

R = methyl).[17-19] The enhanced photodegradability of poly(MEA) can be explained within this framework by the higher thermodynamic instability of this polymer and the ability to unzip more efficiently at lower temperatures. As a result, more efficient "self-amplification" takes place, with each photon being used to cleave a larger number of C-C bonds through depolymerization.

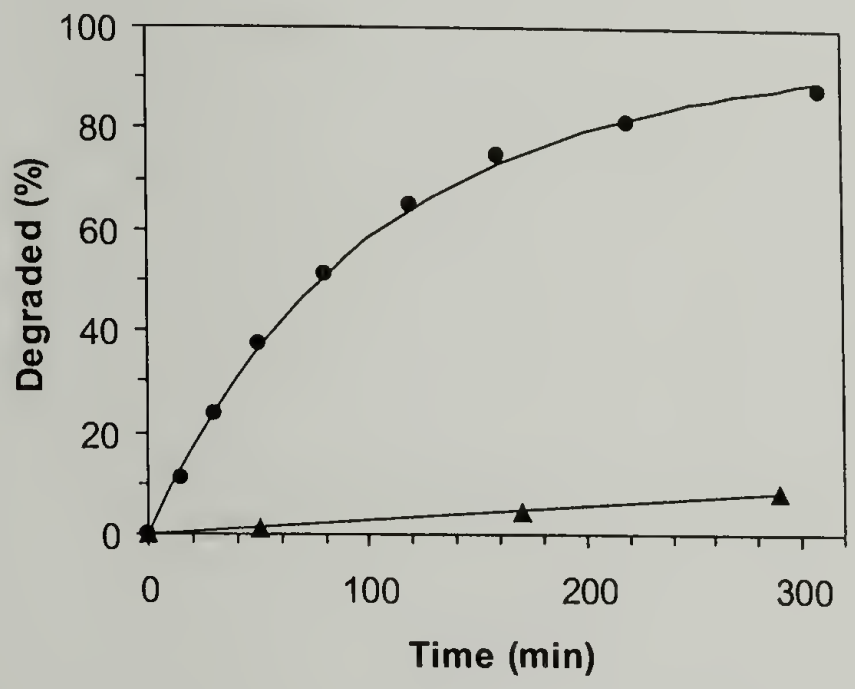


Figure 4.6. Photodegradation of (●) poly(MEA) vs. (▲) PMMA (100 °C, vacuum, UV source: low pressure Hg lamp, degradation monitored as a decrease in the film thickness).

It has been previously shown that the kinetic order of depolymerization n with respect to the sample weight provides a way to distinguish between random ($1 < n \leq 2$) and chain-end ($0 < n \leq 1$) initiation.[20] Data plotted in Figure 4.5 can be used to calculate the order of depolymerization, assuming that the weight loss results entirely from depolymerization. Equation 4.3, which was obtained by integrating the traditional kinetic relationship expressed in Equation 4.5, was used to obtain n.

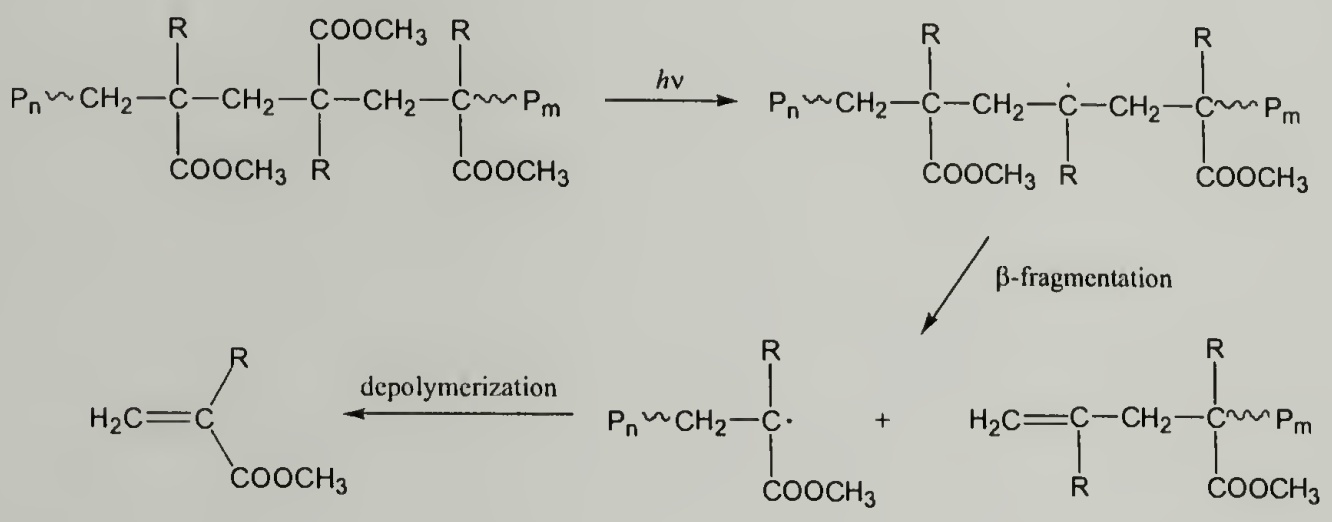
$$C = 1 - (1 + tk')^{1/(1-n)} \qquad (4.3)$$

$$k' = (n - 1)kW_o^{(n-1)} \qquad (4.4)$$

$$-dW/dt = kW^n \qquad (4.5)$$

where C is the conversion to monomer, t is the irradiation time, W is the weight of the sample and k is the rate constant. A non-linear curve fitting procedure (solid line shown in Figure 4.6) provided a value of n equal to 1.24, which suggests that the depolymerization of poly(MEA) is initiated by random bond cleavage.

Scheme 4.3 Photodegradation of poly(methyl α-alkylacrylates).



No photo degradation of poly(M*i*BA) to volatile products could be observed under conditions identical to those used for poly(MEA) and PMMA. To identify whether any degradation was taking place, thicker samples were prepared, irradiated under similar conditions, and analyzed by GPC. The analysis revealed that the molecular weight of the polymer was substantially lowered upon irradiation, decreasing from 179,000 to 25,000 $g \cdot mol^{-1}$ in 3 hours. This result indicates that an efficient chain scission mechanism does occur but does not lead to volatile products under these conditions.

Conclusions

An extensive analysis of structure - thermal property relationships for polymers obtained from α-alkyl acrylates has been achieved. Compared to poly(alkyl

methacrylate)s with the same alkyl group, poly(methyl α-alkylacrylate)s feature degradations that are substantially influenced by the nature of the alkyl group. Steric interactions between adjacent bulky α-substituents decrease the thermodynamic stability of the polymers, and enhance their degradability. For example, changing a methyl by an ethyl dramatically enhanced the photodegradability of the polymers.

Our group is currently investigating means to achieve a living/controlled depolymerization of these metastable polymers by initiating the depolymerization via photo labile and/or redox-active end-groups. External triggers used in this study to initiate degradation of the polymers (heat, 254 nm light) do not provide any selectivity and result in a random bond scission. The synthesis of poly(α-alkylacrylate)s with specific end-groups by living/controlled free-radical polymerization techniques will be described in Chapter 7.

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CHAPTER 5

HIGH-PRESSURE SYNTHESIS AND CONFORMATIONAL BEHAVIOR OF AMPHIPHILIC POLY(α-ALKYLACRYLIC ACID)S

Introduction

Cytoplasmic delivery of therapeutic agents is a crucial part of gene therapy and other intracellular drug delivery processes.[1-3] Foreign bodies, including macromolecular drugs, can be internalized by cells via endocytosis, a process in which a region of the cell membrane invaginates and forms a vesicle encapsulating the small amount of extracellular fluid inside the cell. The so-obtained endosomes are then 'trafficked' to and fused with lysosomes where their contents are subjected to digestion by lysosomic enzymes. Once inside the endosomes or lysosomes, the therapeutic agents have to cross the membranes to reach the cytosol.[4] In particular, sensitive biomolecular therapeutic agents, such as DNAs, RNAs, proteins and peptides, have to be released into the cytoplasm before they reach the lysosomes and are degraded by the lysosomic enzymes.

For that reason, the efficient transport of therapeutic agents from the endosomes/lysosomes to the cytoplasm usually requires the presence of a membrane disrupting agent, inactive in a normal physiological environment and membrane-disruptive at low (endosomal) pH, thus disrupting the endosomal membrane and releasing its contents into the cytosol.[5] This pH-triggered release mechanism is possible because the interior of lysosomes is mildly acidic (pH ≈ 5.0), while for endosomes the pH progressively shifts from neutral to acidic as they are 'trafficked' towards the lysosomes.[6]

Over the years, a number of research groups have designed peptides and synthetic polymers with pH-dependent membrane-disruptive activities to facilitate the endosomal release of therapeutics.[7-18] Poly(α-alkylacrylic acid)s, a class of amphiphilic synthetic polymers, have been investigated in this context for their pH-responsive properties as the balance between the hydrophobic interactions of the alkyl side-groups and the repulsive interactions of the carboxylate substituents on the polymers can be adjusted by controlling the pH of their aqueous solutions. At low pH, hydrophobic groups tend to aggregate, and the polymers adopt compact globule conformations. On the other hand, in high-pH environments, the repulsion between ionized carboxylic groups dominate, and the polymers adopt expanded coil conformations. Poly(methacrylic acid) (PMAA)[19] and poly(α-ethylacrylic acid) (PEAA)[20-22] have been shown to undergo sharp conformational transitions at well-defined pHs whose values depend on the strength of the hydrophobic interactions, i.e. the length of the alkyl groups. Conformational transition of poly(α-alkylacrylic acid)s have also been correlated to their membrane active behavior. Thus, PEAA has been shown to interact with phospholipid bilayers in a pH-dependent manner, showing an increased membrane disruptive activity in acidic environments.[23-26] PEAA and poly(α-n-propylacrylic acid) (PPAA) have been reported to induce red blood cell hemolysis at low pHs, with PEAA displaying maximum hemolysis at pH 5 and PPAA at pH 6.[27,28] Under such acidic conditions, the hemolytic activities of both polymers are equal to or higher than those observed for mellitin, a well-known membrane-disruptive peptide, while at physiological pH, neither one of these polymers is lytic. In addition, PPAA has been shown to retain its pH-dependent activity when 'complexed' to a protein.[29] The possibility to regulate the biological response by playing with the size of

the lipophylic alkyl side-chain and the results already obtained clearly make poly(α-alkylacrylic acid)s potentially useful as pH-responsive membrane disrupting agents for facilitating intracellular delivery of biomolecular drugs.[7,10,28,30-32]

Despite this interest and the need to control the nature and molecular-weight distribution of the polyelectrolyte in order to optimize the physiological effects described in the previous paragraphs, none of the traditional polymerization techniques has proved entirely appropriate to obtain poly(α-alkylacrylic acid)-containing (co)polymers of well-controlled structures. The direct synthesis of poly(α-alkylacrylic acid)s can only be accomplished by a free-radical polymerization of the corresponding acid. Due to the bulky nature of the alkyl group (when larger than a methyl), the polymerization of these monomers is usually slow and does not lead to high-molecular weight polymers. [33,34] In addition, the low polymerizability prevents the use of traditional living polymerization protocolsneeded to achieve control of polymer molecular weights, polydispersities, and end-groups. This particular aspect of our work (controlled polymerization of α-alkylacrylic acid monomers and derivatives) will be treated in Chapter 8.

In this chapter, we will describe our studies on the free-radical polymerization of α-alkylacrylic acids under high pressure conditions in an attempt to improve their polymerizabilities, lead to high-molecular weight polymers, and make these monomers amenable to living polymerization techniques. The conformational behavior of the obtained homo- and co-polymers in aqueous solutions is also presented, and compared to results previously described in the literature.

Experimental Section

Materials. All chemicals were purchased from Aldrich. 2,2'-Azoisobutironitrile (AIBN) was recrystallized from methanol; all other chemicals were used as received. Methyl α-alkylacrylates were synthesized as described in Chapter 2. α-Alkylacrylic acids were obtained by alkaline hydrolysis of the corresponding methyl esters.[35]

α-Ethylacrylic acid (EAA): bp 103 °C at 37 Torr. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 1.11 (t, J = 7.4 Hz, 3H), 2.34 (q, J = 7.4 Hz, 2H), 5.66 (s, 1H), 6.30 (s, 1H), 12.1 (br s, 1H).

α-*n*-Propylacrylic acid (PAA): bp 100 °C at 12 Torr. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.94 (t, J = 7.3 Hz, 3H), 1.52 (m, 2H), 2.28 (t, J = 8.0 Hz, 2H), 5.65 (s, 1H), 6.30 (s, 1H), 12.1 (br s, 1H).

α-*n*-Butylacrylic acid (BAA): bp 112 °C at 12 Torr. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.92 (t, J = 7.2 Hz, 3H), 1.36 (m, 2H), 1.48 (m, 2H), 2.31 (t, J = 7.6 Hz, 2H), 5.65 (s, 1H), 6.30 (s, 1H), 12.1 (br s, 1H).

α-Dodecylacrylic acid (DAA): mp 44-46 °C. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.88 (t, J = 6.4 Hz, 3H), 1.26 (m, 18H), 1.48 (m, 2H), 2.30 (t, J = 7.3 Hz, 2H), 5.64 (s, 1H), 6.28 (s, 1H).

Polymerizations at High Pressure. Polymerizations were carried out in 2 mL Teflon ampoules in a high-pressure reactor purchased from the High Pressure Research Center of the Polish Academy of Sciences. The equipment includes a hydraulic press model LCP20 and a pressure reaction vessel equipped with a temperature controller. N,N-Dimethylformamide (DMF) was used as solvent, and AIBN as the free-radical initiator. Monomers and solvent were deoxygenated by bubbling with nitrogen for 10-15

minutes prior to polymerization. All polymers, except for poly(α-dodecylacrylic acid) (PDAA), were isolated by first removing DMF under vacuum, then diluting with methanol, and finally precipitating into diethyl ether. PDAA was precipitated directly from the DMF solution into methanol. Yields were determined gravimetrically.

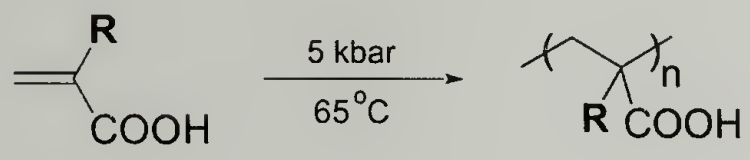
Polymer Characterization. The molecular weights of the polymers were determined by GPC using a HP 1050 HPLC pump, a HP 1047A RI detector, and a three-column set (PLgel, 5 μm, 1x 50 Å and 2x MIXED-D). Measurements were conducted at 1.0 $mL \cdot min^{-1}$ in DMF (0.01 $mol \cdot L^{-1}$ LiCl), and the system was calibrated with narrow polystyrene standards. The aqueous GPC setup consisted of a Kratos Spectroflow 400 Pump, a Shimadzu RID-6A RI detector, and a TSK-GEL column set (2x GMPWXL, 1x G3000PWXL, and 1x G2000SW). A phosphate buffer (0.035 $mol \cdot L^{-1}$, pH = 8.2, I = 0.4) was used as eluent at a flow rate of 1.0 $mL \cdot min^{-1}$. The system was calibrated with narrow poly(ethylene oxide) standards. All ^1H NMR spectra were recorded on a 300 MHz Bruker DPX spectrometer.

Fluorescence Measurements. The conformational state of poly(α-alkylacrylic acids) in aqueous solution was monitored by observing the fluorescence of co-dissolved pyrene. Samples for fluorescence measurements were prepared by mixing 0.5 mL of polymer stock solution (polymer: 4 $mg \cdot mL^{-1}$, pyrene: 200 $\mu mol \cdot L^{-1}$, phosphate buffer: 5 $mmol \cdot L^{-1}$, pH = 8.0) with 1.5 mL of phosphate buffer (pH = 5.40 – 7.90, 0.1 $mol \cdot L^{-1}$, I = 0.3). Pyrene was excited at 337 nm, and the intensities of the fluorescence emission at 373 nm (peak I) and at 384 nm (peak III) were measured using a Perkin Elmer Luminescence Spectrometer LS50B.

Results and Discussion

Polymer Synthesis. Poly(α-alkylacrylic acid)s were obtained by AIBN-initiated free-radical polymerization of the corresponding monomers in DMF solutions at a 5 kbar hydrostatic pressure (Scheme 5.1). Polymers obtained from short chain α-alkyl acids were soluble in DMF and methanol, and dissolved in water in the form of their sodium salts. PDAA was soluble in DMF but not in methanol, and did not dissolve in basic water even after prolonged heating (pH = 10, 80 °C, 16 hours).

Scheme 5.1 α-Alkylacrylic acids.



Acid	R
EAA	$-CH_2CH_3$
PAA	$-CH_2CH_2CH_3$
BAA	$-CH_2(CH_2)_2CH_3$
DAA	$-CH_2(CH_2)_{10}CH_3$

Table 5.1. Polymerization of α-alkylacrylic acids at high and atmospheric pressures.[a]

Monomers	P (kbar)	[M]	[M]/[AIBN]	Time (min)	Conv. (%)	M_n ($\times 10^3$)[b]
EAA	5	4.9	200	225	41	206
PAA	5	4.2	200	265	29	101 (137)[c]
BAA	5	3.6	200	210	19	140
DAA	5	6.2	200	265	12	50
EAA/BAA	5	2.4/1.8	200	240	41	31
PAA	0.001	8.4	50	1490	10	69 (18)[c]
BAA	0.001	7.2	50	1455	8	26

[a] T = 65 °C, 50% v/v in DMF.
[b] Obtained by GPC (DMF, 0.01 mol·L^{-1} LiCl) relative to polystyrene standards.
[c] Obtained by aqueous GPC (0.035 mol·L^{-1} phosphate buffer, pH = 8.2, I = 0.4) relative to poly(ethylene oxide) standards.

The polymerization conditions and molecular weight characteristics for the obtained polymers are presented in Table 5.1. Results for polymerizations conducted at

atmospheric pressure are also included for comparison. As shown in the table, the rates of polymerization of α-alkylacrylic acids were dramatically higher at high pressures. For example, the polymerization of PAA was about 50 times faster at 5 kbar than at ambient pressure, an increase comparable to the effect previously observed for the polymerization of α-alkylacrylic acid esters (see Chapter 2).

The molecular weights of the polymers were characterized by GPC relative to polystyrene standards. Measurements conducted in DMF containing 0.01 $mol \cdot L^{-1}$ LiCl showed a general trend of higher molecular weight polymers being obtained under high-pressure conditions (Table 5.1). However, for PPAA, the increase in molecular weight measured by GPC was very subtle. Earlier studies by Linhardt [36] had shown that GPC characterization of PEAA in DMF provided unusual results with different molecular weight polymers eluting at the same time. This peculiar behavior was attributed to the presence of retention factors not related to size exclusion such as the adsorption of the polymer to the columns or aggregation phenomena. It seems reasonable to assume that similar effects are taking place here despite the use of LiCl in the eluting phase. In agreement with this hypothesis, GPC measurements conducted in water (phosphate buffer, pH = 8.2) relative to poly(ethylene oxide) standards revealed a much larger difference between the two PPAA samples (see Table 5.1). For PBAA, GPC results (in DMF) showed a large difference between samples synthesized at high and atmospheric pressures. This contrasting behavior between PPAA and PBAA can be tentatively rationalized according to the following explanation: as the size of the pendant alkyl group becomes larger and the polymer shows a more hydrophobic character, it gets better solvated by DMF and adsorption/aggregation effects become negligible.

Conformational Transition in Poly(α-Alkylacrylic Acid)s. The pH-dependent conformational behavior of poly(α-alkylacrylic acid)s in aqueous solutions was investigated by fluorescence spectroscopy. It had previously been shown that the fluorescence emission of pyrene is dependent on the polarity of the surrounding medium.[37] In particular, the ratio between peaks III (at 384 nm) and I (at 373 nm) in the pyrene emission spectrum offers a reliable measure of the solvent polarity, with values ranging from 0.63 in water to 1.65 in hexane. This simple approach provides an indirect way to distinguish between expanded coil and compact globule conformations for poly(α-alkylacrylic acid)s, using pyrene molecules as a probe. When the polymer is in a compact globule conformation, pyrene prefers to partition inside the hydrophobic pocket provided by the alkyl groups of the polymer, while, when the polymer adopts an expanded coil conformation, no hydrophobic pocket are available to solubilize the pyrene, which ends up surrounded mostly by water molecules.

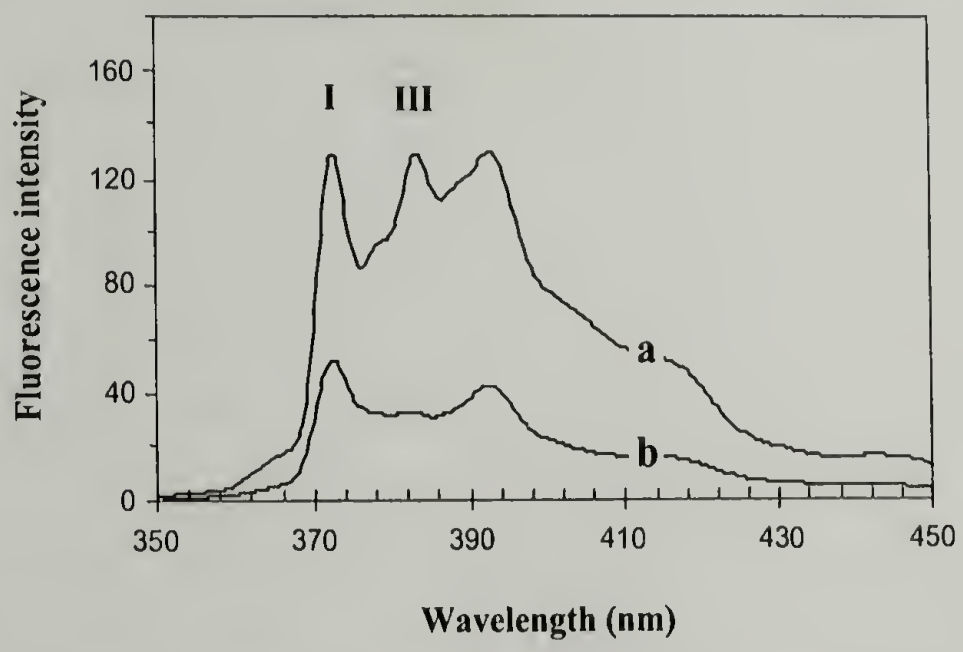


Figure 5.1. Pyrene emission spectra in aqueous solution of PEAA at pH of 5.5 (a) and 6.5 (b).

The fluorescence emission spectra of pyrene co-dissolved with PEAA in aqueous solutions of different pH are shown in Figure 5.1. The fluorescence intensities of a pyrene co-dissolved with different poly(α-alkylacrylic acid)s of increasing alkyl length are shown in Figure 5.2 as a function of the pH. As shown in this figure, all of the investigated polymers, except for PBAA, show relatively sharp coil-to-globule transitions. When the polymers are in expanded coil conformations, the fluorescence emission of pyrene is equivalent to what is observed in water in the absence of any polymer. In contrast, when the polymers adopt compact globule conformations, the fluorescence of a co-dissolved pyrene approaches the value observed in hexane. However, no direct correlation could be observed with a simple hydrophobicity scale based on the length of the alkyl groups.

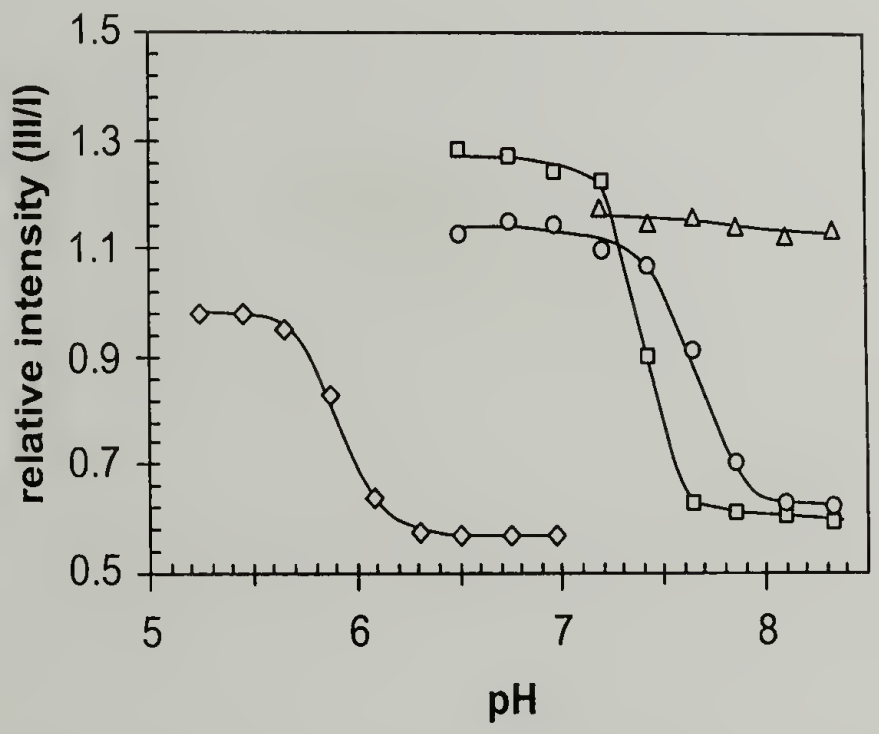


Figure 5.2. Fluorescence intensity of pyrene (Peak III / Peak I) in aqueous solutions of poly(α-alkylacrylic acid)s as a function of the pH: (◊) poly(EAA), (□) poly(PAA), (Δ) poly(BAA), (○) poly(EAA-co-BAA).

The conformational transition of PEAA is narrower and shifted to slightly higher pHs than for PEAA samples synthesized at atmospheric pressure by Linhardt *et al.*.[34] In fact,

the transition curve is very similar to what these authors observed for fractionated PEAA samples of the highest molecular weight (M_n = 16,000 g·mol^{-1}, relative to PEO standards), suggesting that the PEAA sample synthesized at high pressure, despite its polydispersity, does not contain appreciable amounts of low-molecular weight oligomers and has already the range of molecular weights where the transition pH becomes independent of the polymer chain length.

Mid-point transition pH values for poly(α-alkylacrylic acid)s are summarized in Table 5.2. As shown in the table, the transition is extremely sensitive to the length of the alkyl group. An increase in size from an ethyl to a propyl for the α-alkyl group shifts the transition pH by 1.5 units. For PBAA, hydrophobic interactions between butyl groups are so strong that the polymer maintains a globular conformation even at the highest pH investigated. From the available data, it was not possible to conclude whether the PBAA transition, if any, might occur at even higher pH.

In order to gain a precise control over the transition pH and the ability to fine tune its value, copolymers of α-alkylacrylic acids with different alkyl groups can be used. In one such attempt, we synthesized a poly(EAA-co-BAA) copolymer by polymerizing a 50:50 v/v (molar ratio of EAA:BAA = 57:43) mixture of the corresponding monomers. Based on the ^{1}H-NMR data, the copolymer obtained in 41% conversion contained 65% of ethyl and 35% of butyl groups. Taking into account the similar structure of these monomers and their expected similarity in reactivity under high pressure conditions, it seems reasonable to assume that predominantly random copolymers are obtained under these conditions. The synthesized copolymer underwent a conformational transition at a pH of 7.7 (Figure 5.2). The transition curve was slightly broader than what had been observed

for the homopolymers, probably due to a random distribution of alkyl groups among the copolymer chains. Interestingly, the copolymer underwent a transition at a slightly higher pH than PPAA despite having a lower total hydrophobic content. This behavior can be rationalized if one accepts that interactions between long butyl groups are stronger than what would be expected based solely on the hydrophobic content, a conclusion that might be explained either by the cooperative nature of the interactions or by the fact that methyl and methylene segments located further from the backbone are more available for Van der Walls interactions.

Table 5.2. Transition pH values for poly(α-alkylacrylic acid)s.

Alkyl group	Transition pH
Methyl	5.0 [a]
Ethyl	5.9
Propyl	7.5
Butyl	-
Ethyl/butyl	7.7

[a] From Ref. [19].

Conclusions

Poly(α-alkylacrylic acid)s with alkyl groups of increasing length have been synthesized under high pressure conditions. The rates of polymerization and polymer molecular weights were much higher than those obtained from polymerization at atmospheric pressure. Conformational transitions measured for the obtained poly(α-alkylacrylic acid)s in aqueous solutions were investigated by fluorescence spectrometry using pyrene as an external probe. The transition pH was very sensitive to the length of the alkyl pendant group, with PEAA undergoing a transition at a pH of 5.9, and PPAA at 7.4.

Random copolymers of ethyl- and butyl-substituted acrylic acids have also been synthesized. A copolymer containing 65% of α-ethyl groups and 35% of butyl groups has been shown to undergo a conformational change at a pH of 7.9, slightly higher than for PPAA. Initial studies on the biological effect of these polymers have been performed by Lucile Dieudonné in our group and Dr. David Gross in the Biochemistry and Molecular Biology department, and will not be reported here.

Acknowledgements. Lucile Dieudonné is gratefully acknowledged for her contributions to this work.

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CHAPTER 6

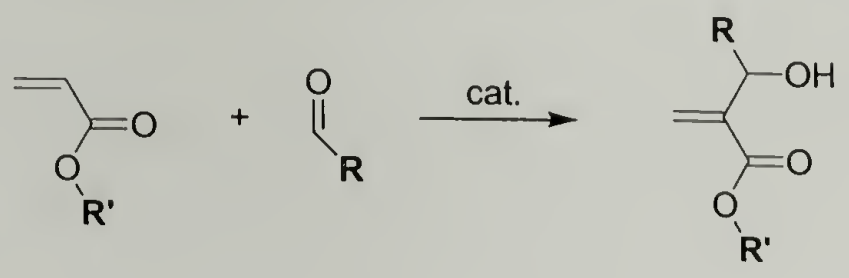
POLYMERIZATION OF FUNCTIONAL α-SUBSTITUTED ACRYLATES DERIVED FROM BAYLIS-HILLMAN ADDUCTS

Introduction

The synthesis of novel functional polymers with inereasing degree of eomplexity relies on the design of more structurally versatile yet simple monomerie building blocks. α-Substituted acrylates obtained by the Baylis-Hillman protocol[1] possess both of these qualities (Scheme 6.1). Struetural versatility is achieved in this case by the presence of two tunable functional groups, the ester group and the easily modifiable α-substituent. The potential of these prospective monomers is further enhaneed by the faet they are easily synthesized in a single step from an aerylate and an aldehyde (Baylis-Hillman reaction). Recent developments in the Baylis-Hillman chemistry open the way to a variety of α-substituted acrylates that can be obtained in high yields.[1] Both R and hydroxy groups on the α-substituent can be used to obtain a moleeule with different functionalities. In addition, the configuration of the asymmetric carbon next to the double bond can be controlled by using chiral catalysts during the Baylis-Hillman synthesis.[2-5] This approach provides a convenient route to introduee side-ehain ehirality into a polymeric structure. Another attractive feature of these monomers is the very elose proximity of the asymmetric center to the reactive double bond, and therefore to the free-radical center during polymerization. For small molecules, it has been shown that providing a chiral environment close to the reaetive free-radieal center can lead to stereoselectivity.[6] In the case of polymers, only a few examples have been described

with a ehiral auxiliary group attached to a monomer, leading to the formation of predominantly isotactic polymers.[7,8]

Scheme 6.1 The Baylis-Hillman reaction.



The polymerization of one system, methyl α-(1-hydroxymethyl)acrylate (R = H), has been studied in detail despite the fact that this monomer is (by far) the most difficult to synthesize and purify.[9] It also does not eontain a ehiral center. High-molecular weight polymers have been synthesized and eharaeterized from both the monomer itself and a variety of ether[10,11] and ester[12,13] derivatives. Attempts to expand the scope of the polymerization by changing the R group from a hydrogen to a methyl or phenyl dramatieally deereased the polymerizability, with only low-molecular weight oligomers forming after extended reaction times.[9] This behavior is basieally similar to what can be observed for α-alkylaerylates, where any monomer with an α-substituent larger than a methyl is diffieult to polymerize.[14] The rationale explaining this dramatic decrease in reactivity has already been exposed in previous chapters, and will not be repeated here.

In this ehapter, the high-pressure polymerization of methyl α-(1-hydroxyethyl)aerylates (R = Me) and some ester derivatives is deseribed. We have previously shown that high pressure aets as a kinetie and thermodynamie driving foree and ean be used to effectively polymerize α-alkylaerylates with bulky α-substituents (see Chapter 2). Chiral derivatives of these monomers were also synthesized by an

asymmetric Baylis-Hillman reaction. Their polymerization and the effect of chiral groups on the stereoselectivity of the propagation step are also investigated.

Experimental Section

Materials. All chemicals were purchased from Aldrich Chemical. 2,2'-Azobis(isobutyronitrile) was recrystallized from methanol; all other chemicals were used as received.

Methyl α-(1-hydroxyethyl)acrylate (**1**). Methyl acrylate (45.0 mL, 0.5 moles), acetaldehyde (22.4 mL, 0.4 moles) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 4.5 g, 0.04 moles) were stirred at room temperature for 7 days. The excess methyl acrylate was evaporated under vacuum and 100 mL of diethyl ether were added. The mixture was washed with 100 mL of 1 mol·L^{-1} HCl, 100 mL of saturated $NaHCO_3$, 100 mL of brine, and then dried over $MgSO_4$. The solvent was evaporated, and the product distilled at reduced pressure (bp 62 °C at 4 Torr, yield = 53 %). ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 1.39 (d, J = 6.5 Hz, 3H), 2.78 (d, J = 5.6 Hz, 1H), 3.79 (s, 3H), 4.69 (m, 1H), 5.84 (s, 1H), 6.22 (s, 1H).

Methyl α-(1-acetoxyethyl)acrylate (**2**). Concentrated H_2SO_4 (1 drop) was added to a mixture of **1** (5 mL, 0.040 moles) and acetic anhydride (7 mL, 0.074 moles). The mixture was stirred at room temperature for 2 hours, and 10 mL of water was added. The product was extracted with ether, and dried over $MgSO_4$. The solvent was evaporated, and the product distilled at reduced pressure (bp 63 °C at 3 Torr, yield = 72 %). ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 1.41 (d, J = 6.5 Hz, 3H), 2.08 (s, 3H), 3.79 (s, 3H), 5.71 (q, J = 6.5 Hz, 1H), 5.83 (s, 1H), 6.29 (s, 1H).

(3S, 8R, 9S)-10, 11-Dihydroxy-3, 9-epoxy-6' -hydroxycinchonane (**3**). The procedure reported in Ref. 4 was followed. The product obtained after column chromatography was recrystallized three times from a MeOH/H_2O mixture (dissolve in minimum amount of MeOH, add H_2O dropwise until crystals start to appear, let it stand overnight at room temperature) to give clear, slightly yellowish, needle crystals.

R -Hexafluoroisopropyl α*-(1-hydroxyethyl)acrylate* (**4**). A mixture of hexafluoro isopropyl acrylate (7.52 mL, 0.045 moles), acetaldehyde (1.96 mL, 0.035 moles) and **3** (0.25 g, 0.806 mmol) in 70 mL of DMF were stirred at –58 °C for 46 hours. The reaction was quenched by 0.1 $mol{\cdot}L^{-1}$ HCl (3 mL), and the product extracted with ethyl acetate. The collected organic fractions were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (SiO_2, Et_2O:hexane = 1:3 (v:v)) to afford **4** in 25 % yield. ^1H NMR ($CDCl_3$, TMS, δ, ppm): 1.42 (d, J = 6.4 Hz, 3H), 2.12 (d, J = 5.4 Hz, 1H), 4.72 (m, 1H), 5.85 (sept, J = 6.1 Hz, 1H), 6.17 (s, 1H), 6.48 (s, 1H).

R -Methyl α*-(1-acetoxyethyl)acrylate* (*R*-**2**). A mixture of **4** (0.922 g, 3.46 mmoles) and NaOMe (37.4 mg, 0.69 mmoles) in MeOH (3.5 mL) was stirred at room temperature overnight. The reaction was quenched by adding Dowex 50 (H^+ form, 250 mg). The mixture was filtered, concentrated, dissolved in ether and passed through a silica column. After evaporating ether, 0.440 g of *R* -methyl α-(1-hydroxyethyl)acrylate was obtained (yield = 97%). It was then subjected to the esterification with acetic anhydride following the procedure described for the synthesis of **2**. The product was purified by column chromatography (SiO_2, EtAc : hexane = 1:3, yield = 51 %, 95 % ee). ^1H NMR ($CDCl_3$,

TMS, δ, ppm): 1.40 (d, J = 6.5 Hz, 3H), 2.08 (s, 3H), 3.78 (s, 3H), 5.72 (q, J = 6.5 Hz, 1H), 5.82 (s, 1H), 6.29 (s, 1H).

Polymerizations at High Pressure. Polymerizations were carried out in 2 mL Teflon ampoules in a high-pressure reactor purchased from the High Pressure Research Center of the Polish Academy of Sciences. The equipment included a model LCP20 hydraulic press and a pressure reaction vessel equipped with a temperature controller. Monomers were deoxygenated by bubbling with nitrogen for 10-15 minutes prior to polymerization. At the end of the polymerizations, the remaining monomer was removed in *vacuo*, the polymers dissolved in tetrahydrofuran and precipitated in hexanes. Yields were determined gravimetrically.

Measurements. Molecular weights of the polymers were determined by gel permeation chromatography (GPC) with a Waters 510 HPLC pump, Waters R400 Differential Refractometer detector, and three PLgel columns (5 μm, 1x 50 Å and 2x MIXED-D). The system was calibrated with narrow polystyrene standards. High-temperature NMR spectra of the polymers were recorded at 150 °C in d_5-nitrobenzene using a Bruker Avance 600 spectrometer operating at 600.03 MHz (^{1}H) and 150.88 MHz (^{13}C). For ^{1}H NMR analysis, samples with a concentration of 10 mg·mL^{-1} were used and chemical shifts were referenced to the most upfield solvent resonance of nitrobenzene at 7.50 ppm. ^{13}C NMR spectra were recorded under proton decoupling at a concentration of 100 mg·mL^{-1} and chemical shifts were referenced to the most upfield peak of the solvent resonance at 123.5 ppm. Conditions for the ^{13}C NMR experiments were not optimized for quantitative analysis. A DEPT experiment was used to determine the multiplicity of the carbons in the ^{13}C spectra. Room-temperature NMR analysis was performed on a

Bruker DPX 300 spectrometer, operating at 300.15 MHz (^{1}H). The thermal stability of the polymers was investigated by thermogravimetric analysis (TGA) on a DuPont TA 2050 under nitrogen at a heating rate of 10 $^{o}C{\cdot}min^{-1}$. The glass transitions were determined by differential scanning calorimetry (DSC) using a DuPont 2910 at a heating rate of 10 or 20 $^{o}C{\cdot}min^{-1}$ under nitrogen. Circular dichroism (CD) measurements were conducted on a Jasco J-715 spectropolarimeter.

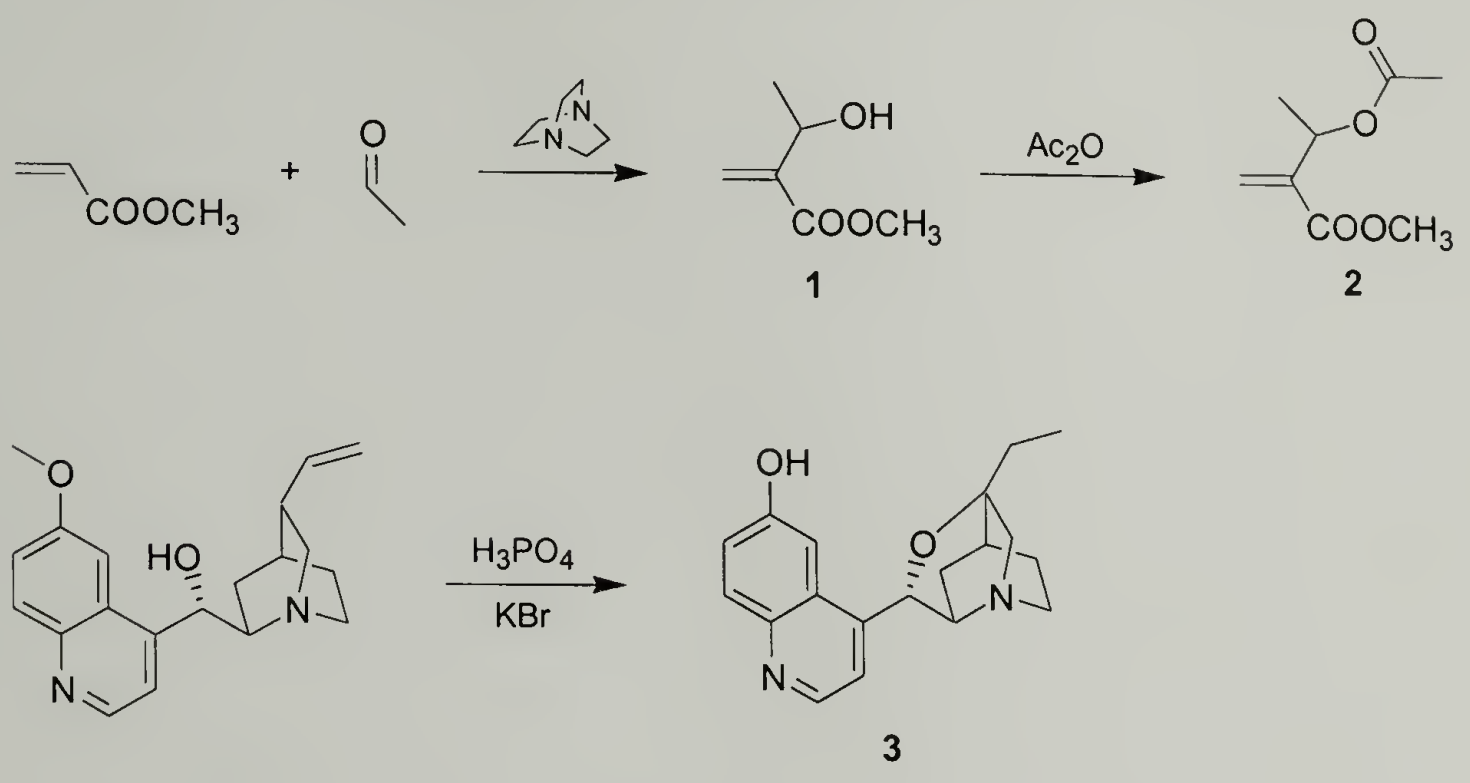
Results and Discussion

Monomer Synthesis. Monomer **1** was synthesized via a DABCO catalyzed Baylis-Hillman reaction between methyl acrylate and acetaldehyde (Scheme 6.2). The reaction was slow but led to high conversions. Attempts to increase the overall rate by lowering the reaction temperature – as reported in the literature[15] – were not successful.

To obtain a chiral version of **1** via an asymmetric Baylis-Hillman protocol, the *Cinchona* alkaloid derivative **3** was used as a chiral catalyst in the reaction. **3** was synthesized in one step starting from quinidine (Scheme 6.2) following the reported procedure[4]. After purification by column chromatography, several recrystallizations from a MeOH-H_2O mixture were necessary to obtain pure crystals of $\mathbf{3}{\cdot}(MeOH)_1{\cdot}(H_2O)_1$ structure.[16,17] The catalyst **3** had been reported to catalyze Baylis-Hillman reactions with very high degrees of enantioselectivity,[4] although the reaction had to be carried out at low temperatures to achieve the highest selectivity. A fluoro-containing, activated acrylate (scheme 6.2) was used as a substrate rather than the simpler methyl acrylate because the reactivity of simple acrylates at these temperatures are prohibitively low. The enantiomeric excess of the obtained chiral acrylate *R*-**2** was determined to be more than 95 %, using ^{1}H NMR in the presence of a $Eu(hfc)_3$ chiral shift reagent.[18,19] The absolute

stereochemical configuration of the monomer was assumed to be *R* based on the information available for similar compounds synthesized using the same catalyst.[4]

Scheme 6.2 Synthesis of α-substituted acrylates by the Baylis-Hillman protocol.



High Pressure Polymerizations. The polymerization of **1** initiated by AIBN at 65 °C and at atmospheric pressure was very slow, reaching 15% conversion in about 50 hours. Surprisingly, the rate of polymerization of **1** increased only slightly when conducted at 5 kbar (Table 6.1). In both cases (atmospheric and high pressures), oligomeric products were obtained as revealed by GPC (relative to polystyrene standards). The molecular weight distributions of the polymers were narrower than expected for an uncontrolled free-radical polymerization, probably due to some

fractionation occurring during the precipitation. When the hydroxyl group in **1** was converted to an acetyl ester, providing monomer **2**, the polymerizability of the acrylate dramatically improved at high pressure. The polymerization at 5 kbar proceeded at a high rate, and resulted in high molecular weight polymers (Table 6.1). No polymerization of **2** could be observed when conducted at atmospheric pressure.

The small effect exerted by the pressure on the polymerizability of **1** compared to the strong effect observed in the case of **2** (i.e. $|\Delta V^{\ddagger}_1| < |\Delta V^{\ddagger}_2|$, see Equation 1.2) can most probably be attributed to the hydrogen bonding capability of **1**. The formation of hydrogen bonds between the approaching monomer and the polymer chain end in the solution, leading to some pre-organization, might, in this framework, lead to a more compact initial state, and decrease the activation volume $\Delta V^{\ddagger}$ of the polymerization.

Table 6.1 Polymerization results for α-substituted acrylates **1**, **2**, and *R*-**2**.[a]

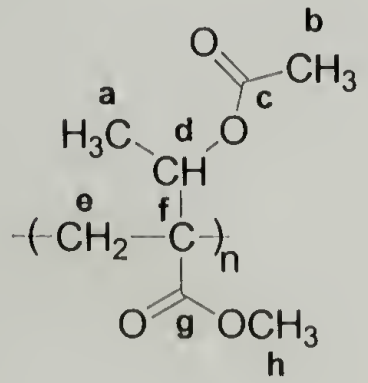
Exp.	Acrylate	[AIBN]	Pressure (kbar)	Time (h)	Conversion (%)	M_n[b] ($\times 10^3$)	M_w/M_n[b]
1	**1**	0.161	0.001	49.5	15	0.8	1.20
2	**1**	0.161	5	37.5	23	0.8	1.38
3	**2**	0.062	0.001	43	0[c]	-	-
4	**2**	0.062	5	17	59	42.2	2.35
5[d]	**2**	0.009	9	22	86	5.8	2.98
6[d]	*R*-**2**	0.009	9	15.5	21	6.6	1.84

[a] $T = 65$ °C, bulk.
[b] Determined by GPC (THF, polystyrene standards).
[c] No precipitation in hexanes.
[d] [Acrylate] = 0.86 mol·L^{-1} in 2-butanone.

The structure of poly(**2**) was carefully analyzed as it had been shown previously (see Chapter 2) that unusual side reactions can take place during the propagation step when the polymerization is coerced by using high pressures. An elemental analysis of poly(**2**)

revealed that the expected composition had been obtained (-$(C_8H_{12}O_4)_n$-, calculated: C% 55.81, H% 7.02; found: C% 55.65, H% 6.95). A ^{1}H NMR spectrum recorded at 150 °C in d_5-nitrobenzene showed broad signals in the region ranging from 1.2 to 4.1 ppm, and additional peaks could be observed in the region between 5.2 and 6.7 ppm (Figure 6.1). The broad signals in the ^{1}H NMR spectrum at such high temperatures is indicative of a restricted mobility for polymeric chain segments, resulting most probably from strong steric interactions between the bulky side substituents. Peaks in the ^{1}H NMR spectrum (Figure 6.1) were tentatively assigned to protons in the structure expected for poly(**2**) (Scheme 6.3).

Scheme 6.3 Poly(methyl α-(1-acetoxyethyl)acrylate).



In the ^{13}C NMR spectrum of poly(**2**), all observed peaks are consistent with the expected structure for poly(**2**). Three different methyl groups (carbon peaks **a**, **b** and **h**) are easily distinguishable (Figure 6.2). In addition, signals for the carbons corresponding to methylene **e** and methine **d** groups, quaternary carbons of the backbone **f**, and the carbonyl groups **c**,**g** can be identified. Carbon multiplicities were assigned based on a DEPT analysis.

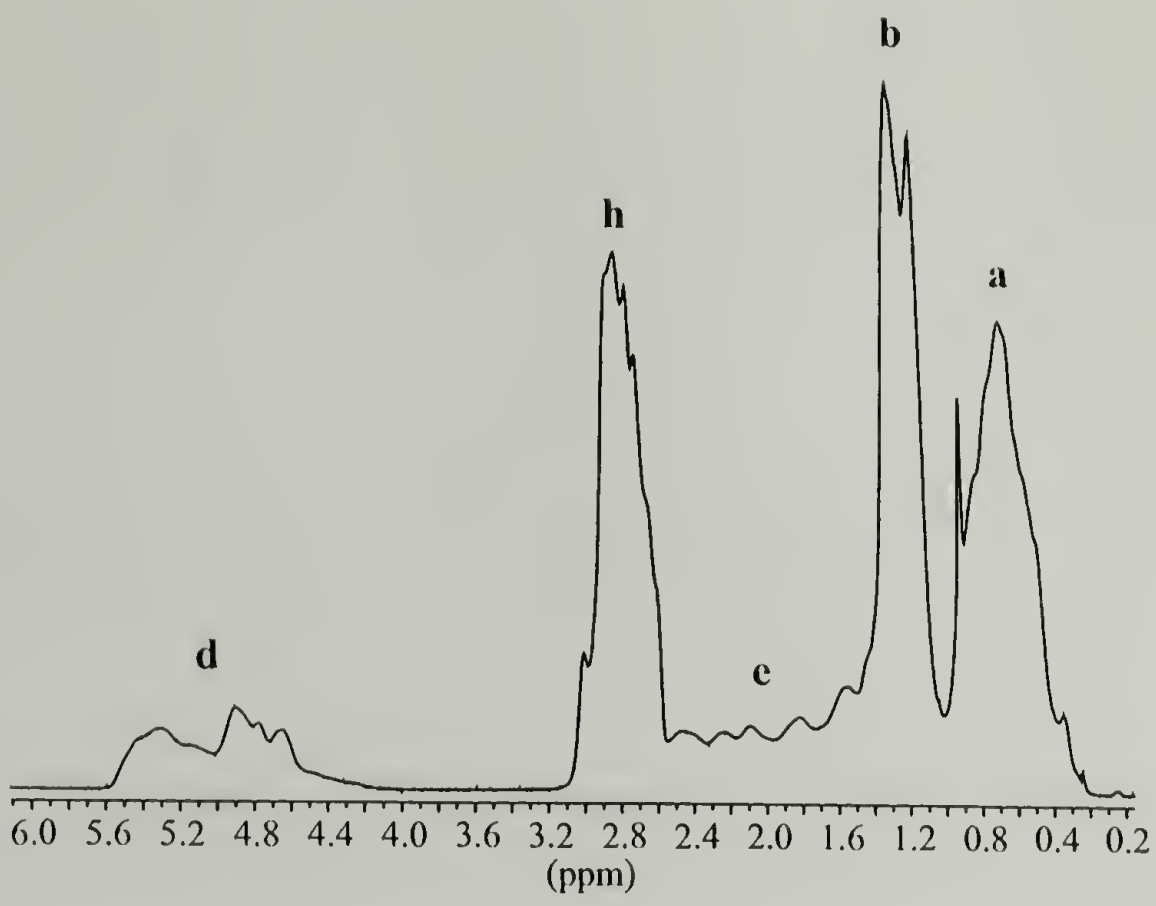


Figure 6.1. ^{1}H NMR Spectrum of poly(**2**) (150 ^{o}C, d_5-nitorbenzene).

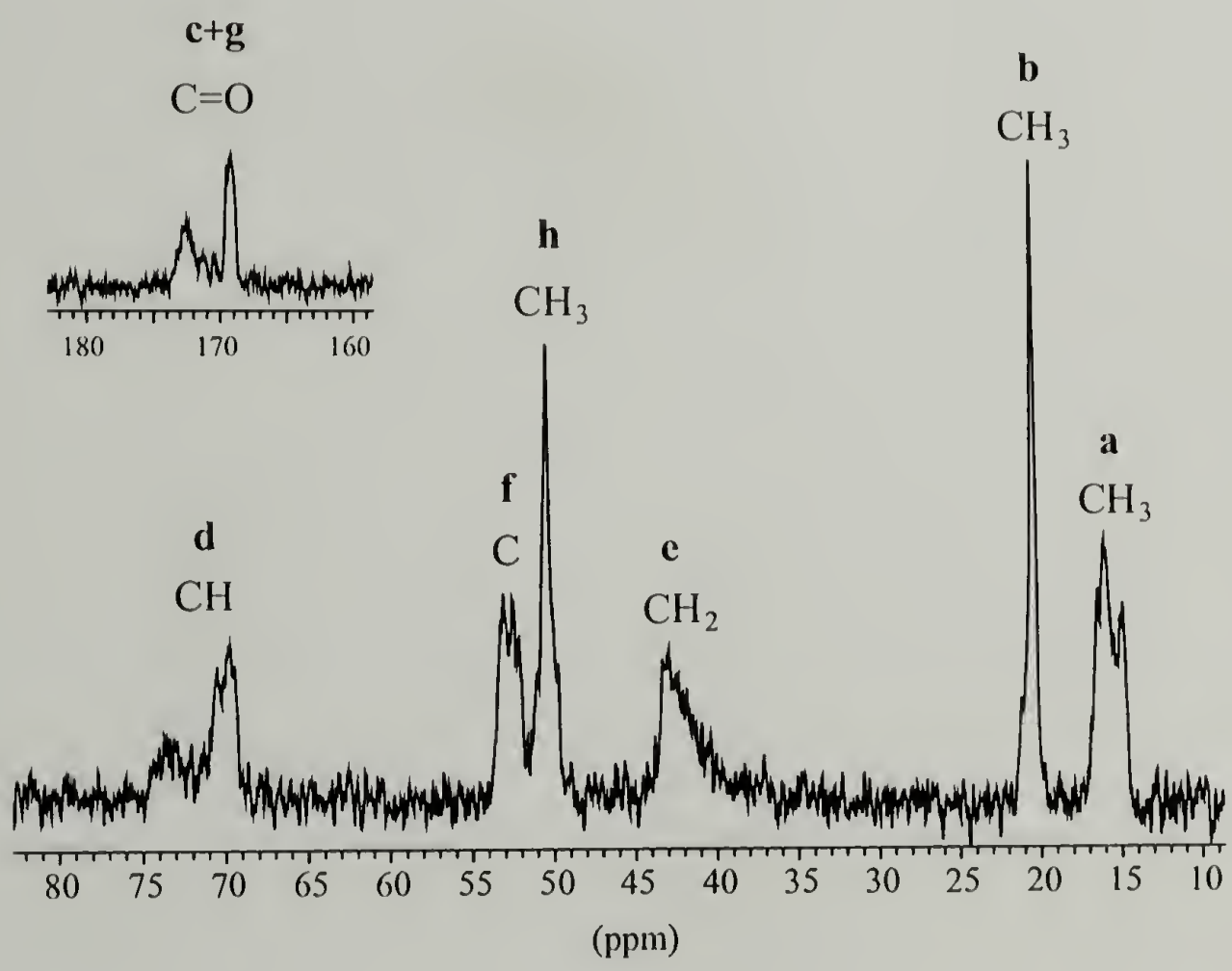


Figure 6.2. ^{13}C NMR Spectrum of poly(**2**) (150 ^{o}C, d_5-nitorbenzene).

Signals in the region between 5.2 and 6.7 ppm in the ^{1}H NMR spectrum were assigned to the methine protons **d** of the α-substituents. When compared to small organic molecules, this is an unexpectedly high chemical shift for such a proton. Normally, signals for olefinic protons show up in this region of the ^{1}H NMR spectrum. However, in the case of polymers, rigid structure of the backbone can sometimes force specific conformations to be adopted, resulting in a completely different electronic environments for certain protons. In addition, the chemical shift of the methine carbon **d** in the ^{13}C spectrum is in the expected aliphatic region, disallowing the presence of an olefinic group in the polymer.

Thermogravimetric analysis of poly(**2**) revealed that the polymer was stable up to 250 °C, and then decomposed at higher temperatures and in a single step to volatile products with zero char yield (Figure 6.3). The decomposition temperature of poly(**2**) was much lower than for poly(methyl methacrylate) but was comparable to other poly(α-alkylacrylates) with bulky alkyl side groups. No glass or other transitions could be detected by DSC up to the decomposition temperature.

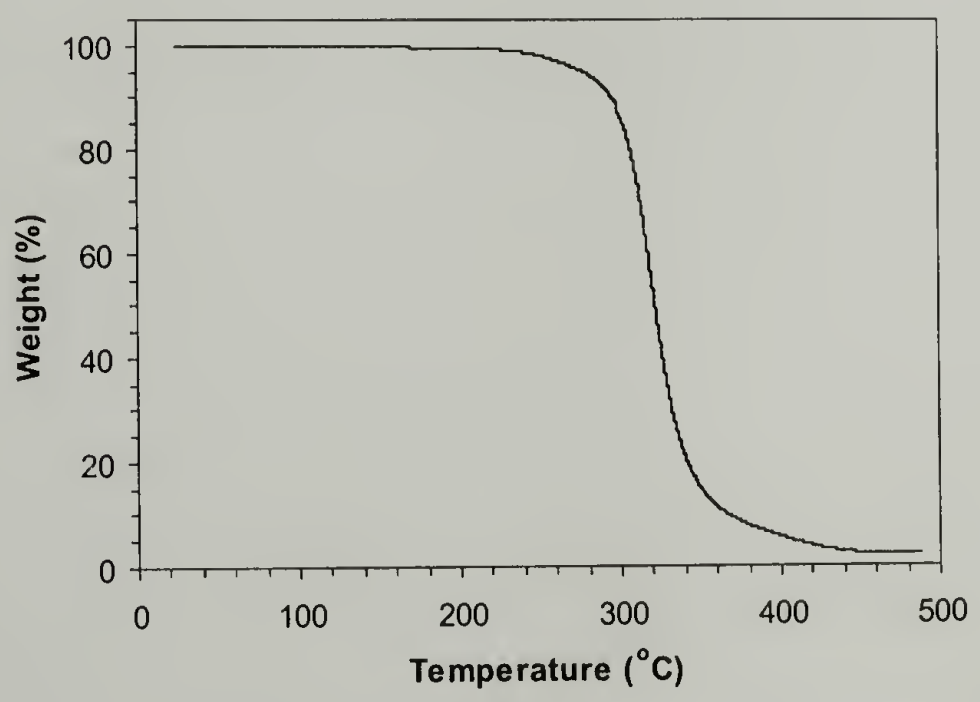


Figure 6.3. Thermogravimetric analysis of poly(**2**) (10 °C min^{-1}, N_2).

Synthesis of Chiral Poly(α-Substituted Acrylates). *R*-**2** was polymerized in a 2-butanone solution at 9 kbar. The polymerization proceeded at fair rate, but resulted in low-molecular weight polymers (Table 6.1). Similar results were obtained when racemic **2** was polymerized under identical conditions, with the molecular weights being much lower than for the polymers obtained at 5 kbar in bulk (Experiment 4 in Table 6.1). These low molecular weights can possibly result from a chain-transfer reaction to the monomer or to the solvent, 2-butanone. Depending on the relative effect of pressure on the rate constants of propagation and chain transfer, it is possible that the ratio between these two coefficients increase under pressure.[20] Another explanation for the low molecular weights obtained in Experiments 5 and 6 (Table 6.1) could be related to the fact that the polymerizations were conducted at low monomer concentrations. The lower monomer concentration diminishes the ceiling temperature T_c,[21] possibly down to the polymerization temperature.

The markedly different ^{1}H NMR spectra of poly(**2**) and poly(*R*-**2**) recorded at room temperature in $CDCl_3$ are displayed in Figure 6.4. In the spectrum of poly(**2**), peaks assigned to methyl groups **a** and **b** consist of a major and a minor components (for **a**: major (1.0-1.4 ppm), minor (1.4-1.7); for **b** (major (2.05), minor (2.16)). In the case of poly(*R*-**2**), the signals from the minor components are significantly larger. In addition, the spectrum of poly(*R*-**2**) shows a better resolution in the signals assigned to the methyl ester group **h**. If the two polymers were only different in the fact that one of them contained α-substituents of both *R* and *S* configuration while the other had only chiral side units of *R* configuration, the spectrum of poly(*R*-**2**) would be much simpler than for poly(**2**). The observed difference between the two spectra suggests that the

stereochemical features associated to the two polymerizations are different. It can be argued that the asymmetric carbon **d** on the α-substituent, being so close to the propagating center, influences the stereochemistry of the monomer addition and therefore the tacticity of the formed polymers, although a complete control of the tacticity, i.e. the formation of a fully isotactic polymer, is not achieved. A more detailed analysis of the polymer microstructures was prohibited by the broadness of the peaks and the resulting poor resolution in the ^{1}H NMR spectra.

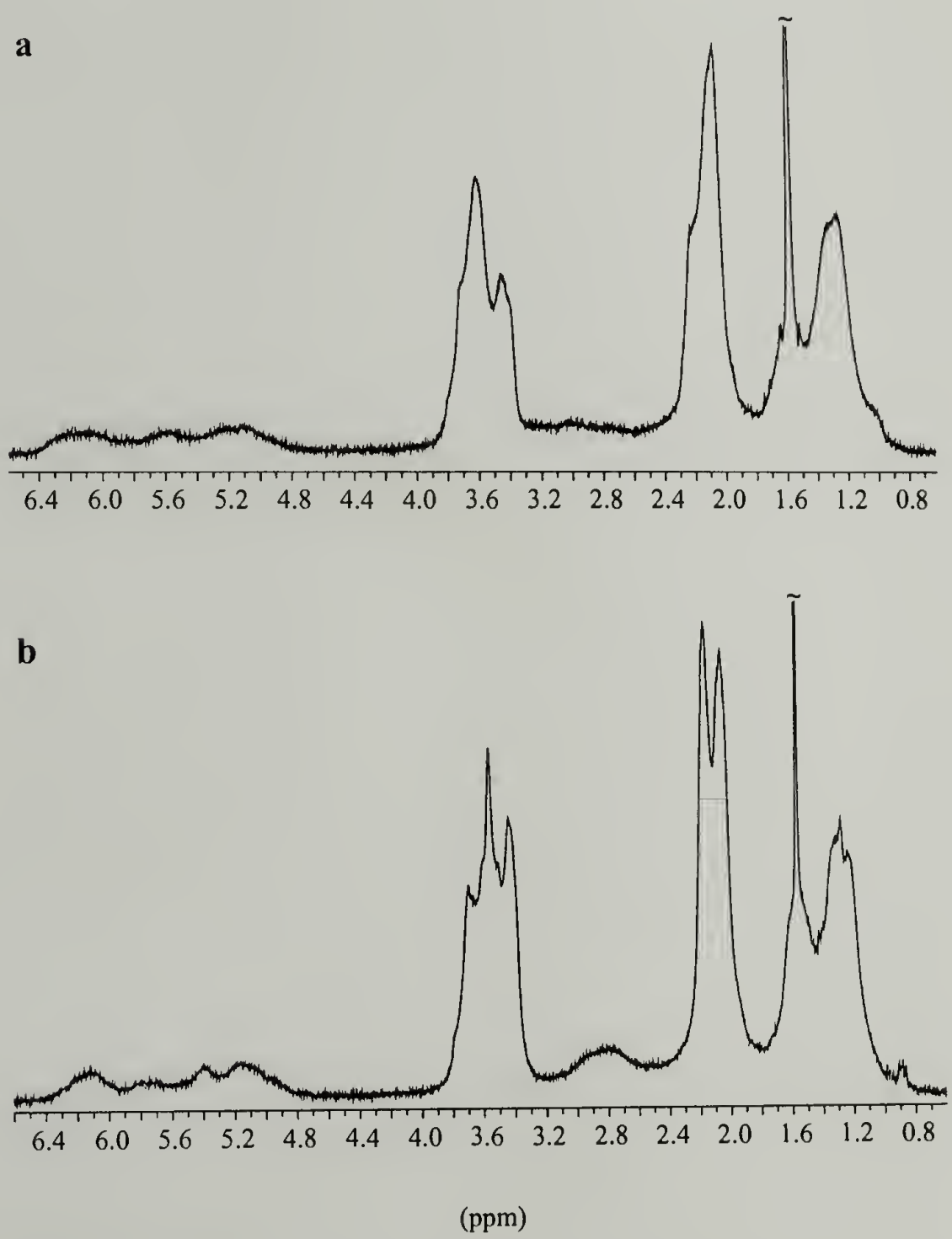


Figure 6.4. ^{1}H NMR spectra (RT, $CDCl_3$) of (a) poly(**2**), and (b) poly(*R*-**2**) synthesized under high pressure conditions (9 kbar, 65 °C, DMF).

The CD spectra in tetrahydrofuran of *R*-**2** and its polymer are displayed in Figure 6.5. As shown in the figure, the intensity of the signal for the polymer is lower than for the corresponding monomer at the same concentration in chiral groups. This result suggests that no stable secondary structure (helix) is obtained for poly(*R*-**2**). This result is not entirely unexpected. The formation of an helical structure is known requires an almost perfect control of the tacticity in a polymer, with even small amounts of defects preventing the formation of well-defined conformations.[22] Within this framework, the lack of a regular secondary structure in poly(*R*-**2**) can be explained by its poorly defined microstructure.

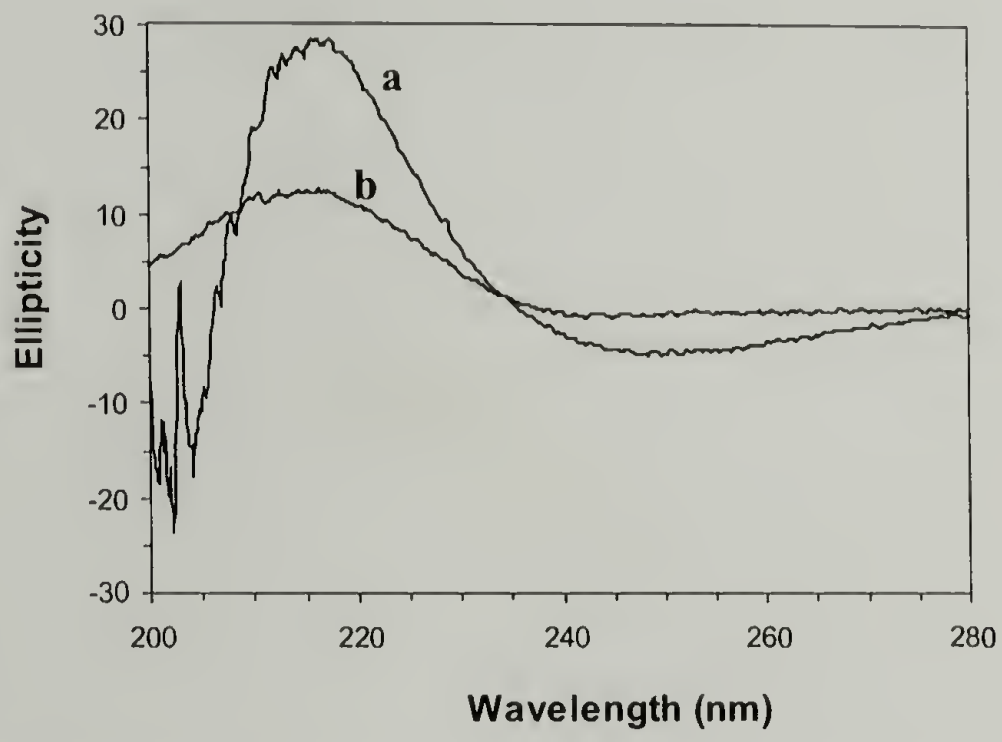


Figure 6.5. Circular dichroism spectra of (a) monomer *R*-**2**, and (b) poly(*R*-**2**) in THF.

Conclusions

The high-pressure polymerization of structurally versatile α-substituted acrylates obtained by a one-step Baylis-Hillman reaction between simple acrylates and aldehydes was investigated. The polymerizability of acrylates containing an hydroxyl group in the α-substituent did not improve with the pressure, while the polymerization of their ester

derivatives was dramatically accelerated under high pressure conditions. A detailed spectroscopic characterization confirmed the structure expected for these polymers.

Chiral acrylates were conveniently synthesized by an asymmetric Baylis-Hillman reaction using the *Cinchona* alkaloid derivative **3** as a catalyst. The polymerization of these monomers at high pressure provided an easy way to chiral polymeric structures. The asymmetric center present on the α-substituent close to the propagating center was shown to affect the microstructure of the formed polymers. A detailed investigation of this effect was prevented by the rigid nature of the polymers and resulting poor resolution of their NMR spectra.

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CHAPTER 7

CONTROLLED/LIVING FREE-RADICAL POLYMERIZATION OF STERICALLY HINDERED ACRYLIC MONOMERS UNDER HIGH PRESSURE

Introduction

Recent progress in "living" free-radical polymerization (LRP) techniques, such as iniferter polymerization,[1] atom-transfer radical polymerization (ATRP),[2-4] nitroxide-mediated radical polymerization[5,6] and reversible addition-fragmentation chain-transfer (RAFT) polymerization,[7-9] has opened new routes for the synthesis of polymers with predefined molecular weights, well-defined end-groups and narrow polydispersities. Controlled/living polymerization techniques are based on a delicate balance between dormant and active species that effectively reduces the concentration of free radicals in the system and minimizes the extent of termination. These 'living' polymerization techniques are based on free-radical intermediates and so, unlike ionic-based systems, are not sensitive to classical impurities or moisture, and are tolerant to various functionalities. These attractive features facilitate the synthesis of well-defined polymers and complex architectures, such as block copolymers, from a great variety of monomers. Until now, LRP techniques have been applied mostly to conventional monomers, such as styrene and (meth)acrylate derivatives, and the polymerizations have usually been conducted under classical free-radical polymerization conditions.[10] Controlled polymerization of monomers that require the use of non-traditional conditions, such as very high pressure, in order to polymerize have not been attempted yet, and optimum experimental

conditions cannot be easily extrapolated from results at ambient pressure due to the sensitivity of LRP techniques to reaction conditions.

The objective of this work is to extend the scope of LRP reactions to monomers that cannot be polymerized under 'normal' conditions for thermodynamic and kinetic reasons. In Chapter 2 we demonstrated that 'non-polymerizable' α-alkylacrylates can easily be polymerized to high molecular weight polymers under high pressure conditions (1-9 kbar). Access to these and structurally related polymers have been sought for quite a long time as they offer interesting perspectives for biomedical and other applications.

In this Chapter, we report the first example of a controlled free-radical polymerization under very high pressure. The RAFT technique was specifically investigated due to its known lower sensitivity to reaction conditions. Methyl ethacrylate (MEA) was selected for this study as a model "non-polymerizable" monomer since its oligo/polymerization kinetics at both ambient and high pressure have been previously investigated. Due to the steric hindrance of its α-ethyl substituent, MEA has a low ceiling temperature (82 °C in bulk monomer at ambient pressure) and is reluctant to polymerize under traditional free-radical conditions.[11] It should be noted that polymerizations under pressures of supercritical carbon dioxide (up to 0.33 kbar) have already been reported.[12,13] However, the highest pressure reported in those studies (4,900 psi = 0.33 kbar vs. 5 kbar used in this study) is not high enough to significantly affect thermodynamic or kinetic parameters of a vinyl polymerization.[14]

Experimental Section

Materials. All chemicals were purchased from Aldrich Chemical Co. 2,2'-Azoisobutironitrile (AIBN) was recrystallized from methanol; all other reagents were

used without further purifieation. Methyl ethaerylate (MEA)[11] and 2-eyanoisopropyl dithiobenzoate (DTB)[9] were synthesized aeeording to literature proeedures.

Polymerizations. Polymerizations were earried out in 2 mL Teflon ampoules in a high-pressure apparatus purehased from the High Pressure Researeh Center at the Polish Aeademy of Seienees. The apparatus ineluded a hydraulie press model LCP20 and a pressure reaetion vessel equipped with temperature eontroller. Polymerization mixtures (monomer, RAFT reagent, AIBN and solvent) were degassed by three freeze-pump-thaw eyeles, and transferred into the Teflon ampoules under nitrogen atmosphere. Polymers were preeipitated in hexanes and dried *in vacuo*. Conversions were determined by ^{1}H NMR.

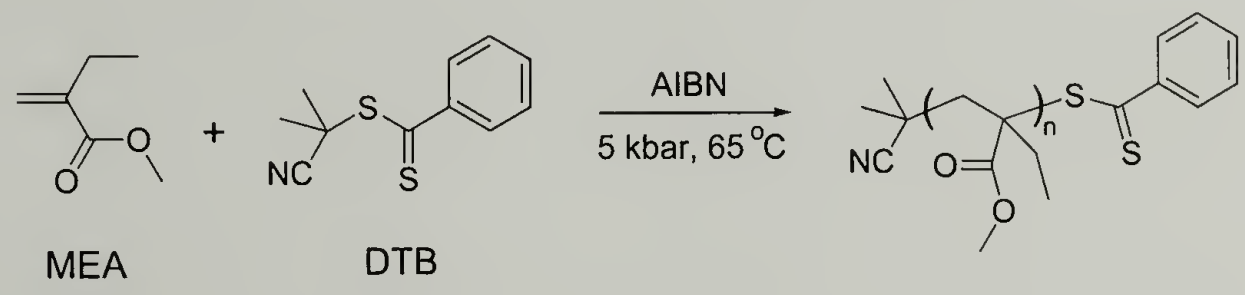
Measurements. Moleeular weights of the polymers were determined by gel permeation ehromatography (GPC) with a Waters 510 HPLC pump, Waters R400 Differential Refraetometer deteetor, and three PLgel eolumns (5 μm, 1x 50 Å and 2x MIXED-D). The system was ealibrated with narrow poly(methyl methaerylate) (PMMA) standards. NMR analysis was performed on a Bruker DPX 300 speetrometer, operating at 300.15 MHz (^{1}H). MALDI-TOF speetra was reeored on Bruker REFLEX III Mass Speetrometer. 2,5-Dihydroxybenzoie aeid was used as a matrix and sodium triflouroaeetate was added as a eation souree. ESI speetra was obtained using Bruker-HP Esquire-LS system. Aeetonitrile was used as a solvent. UV measurements were eondueted on a Hitaehi U-3010 Spectrophotometer.

Results and Discussion

Polymerization Kinetics. High pressure RAFT (HP-RAFT) polymerizations of MEA were carried out in a high-pressure apparatus at 5 kbar and 65 ^{o}C using 2,2'-

azobisisobutyronitrile (AIBN) as the free-radical initiator and 2-cyanoisopropyl dithiobenzoate (DTB) as the RAFT agent (Scheme 7.1). First-order kinetics with respect to monomer concentration was observed, as shown in Figure 1a. A linear relationship was observed throughout the studied region (15 - 75 % conversion), although the intercept of the regression line did not reach the origin. A value of 2.64×10^{-4} $L^{1/2}\cdot mol^{-1/2}\cdot s^{-1}$ for the $R_p[M]^{-1}[I]^{-1/2}$ ratio can be calculated from the straight line, which is close to the number observed under traditional free-radical conditions at 5 kbar (2.80×10^{-4} $L^{1/2}\cdot mol^{-1/2}\cdot s^{-1}$) (see Chapter 2), i.e. the rate of polymerization is not affected by the presence of the RAFT reagent. The decrease in the rate of polymerization, i.e. retardation, has been observed during RAFT polymerization of some monomers, and the effect has been attributed to the slow fragmentation of the polymeric RAFT adduct **2** (Scheme 7.2), which effectively reduces the concentration of propagating free-radicals.[9] Within this framework, it can be concluded that the RAFT reagent DTB behaves as an ideal chain-transfer agent with fast fragmentation step even under 5 kbar pressure.

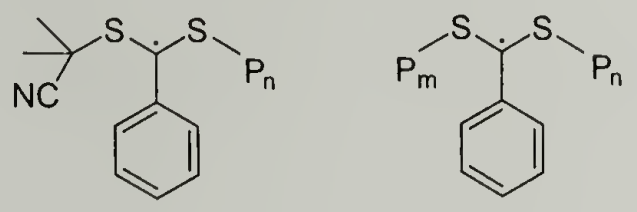
Scheme 7.1 RAFT polymerization of MEA.



An inhibition period similar to the one observed here has previously been reported in the case of a styrene polymerization with cumyl dithiobenzoate as the RAFT agent and was attributed to a slow initiation by the cumyl radical.[9] This clearly cannot be the origin of the initial retardation observed in the present system: the cyanoisopropyl radical,

generated from both the RAFT agent and the initiator, is known to act as an efficient initiating species. It seems more reasonable to attribute the slow initial kinetics to a slower fragmentation of the initial adduct **1** (Scheme 7.2) compared to the fragmentation of adduct **2** that dominates the RAFT process at higher conversion. This difference in reactivity most probably arises from the steric crowding and the resulting difference in stability between **1** and **2**.

Scheme 7.2 Intermediate adducts forming during RAFT polymerization.



1 **2**

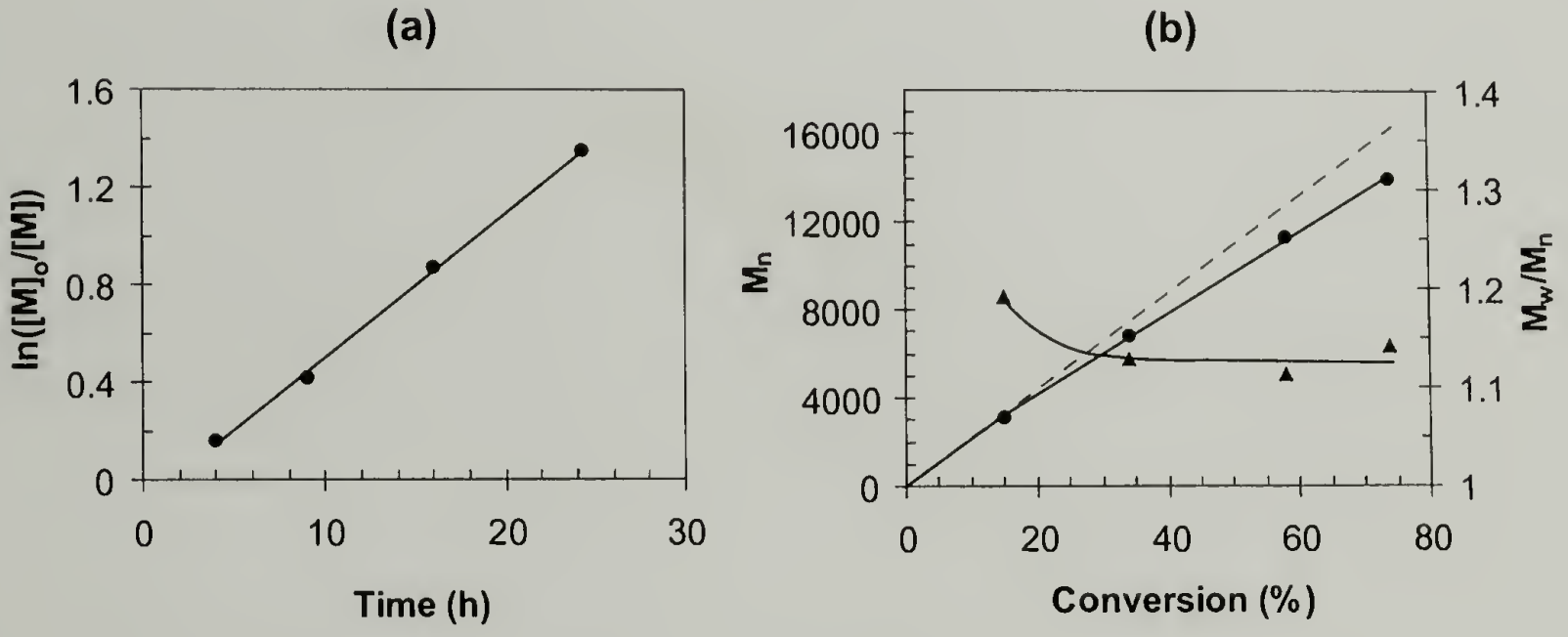


Figure 7.1. Results for the RAFT polymerization of MEA at 5 kbar (T = 65 °C, [MEA]:[DTB]:[AIBN] = 2000:10:1): (a) First-order kinetic plot, (b) Dependence of molecular weights (● $M_{n,exp}$, --- $M_{n,th}$) and polydispersities (▲) on conversion.

The controlled character of the polymerization is consistent with the observed linear increase in molecular weight with conversion (Figure 1b). Relative molecular weights

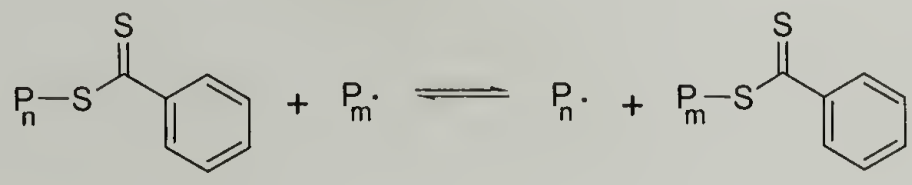
determined by GPC calibrated with PMMA standards were close but consistently lower than the theoretical values calculated from the monomer-to-RAFT-agent molar ratio. Polydispersities remained low (<1.2) throughout the polymerization, decreasing up to 40% conversion and then leveling off (Figure 1b). This last experimental observation indicates the absence of major chain termination events.

Table 7.1. High-conversion RAFT polymerization of methyl ethacrylate MEA under high pressure conditions.[a]

Concentration (mol L^{-1})	*P* (kbar)	Time (h)	Conv. (%)	$M_{n,exp}$[b] ($\times 10^3$)	$M_{n,th}$[c] ($\times 10^3$)	M_w/M_n[b]
8.06 (Bulk)	5	52	88	20.7	20.1	1.51
8.06 (Bulk)	9	3	67	16.8	15.3	1.51
2.64 (DMF)	9	24	98	26.2	22.4	1.12

[a] T = 65 °C, [M]:[DTB]:[AIBN] = 2000:10:1
[b] GPC (PMMA standards)
[c] Calculated from monomer-to-DTB ratio

Scheme 7.3 The RAFT equilibrium.



When polymerization were allowed to proceed to high conversions (up to 88%, which is the highest conversion achievable at this pressure in bulk monomer), polymers with relatively broad molecular weight distributions were obtained, although M_n was still close to the expected value (Table 7.1). Similar results were obtained, even at lower conversions, when the polymerization was carried out at 9 kbar, suggesting that the high viscosity of the system might be responsible for this deviation from ideality. On the other hand, polymerization in a solvent proceeded smoothly to quantitative conversion, even at

9 kbar, and resulted in polymers with low polydispersity indices and expected molecular weights. These results can be explained from the fact that the equilibrium between dormant and active species necessary for an efficient RAFT polymerization is achieved via a reaction involving two polymeric chain-ends (Scheme 7.3). When the viscosity of the system reaches a certain critical value, diffusion of the polymeric chain-ends becomes so slow that reversible chain-transfer becomes too slow compared to propagation, enabling some chains to grow faster than the others and leading to a broader molecular weight distribution. Under this scheme, large polydispersities obtained at high conversions are indicative of a slow equilibrium between dormant and active species and not of a chain-terminating event. It is possible that this phenomenon also affects bulk polymerization carried out to very high conversions at ambient pressure. At high pressures, however, this effect is certainly magnified.

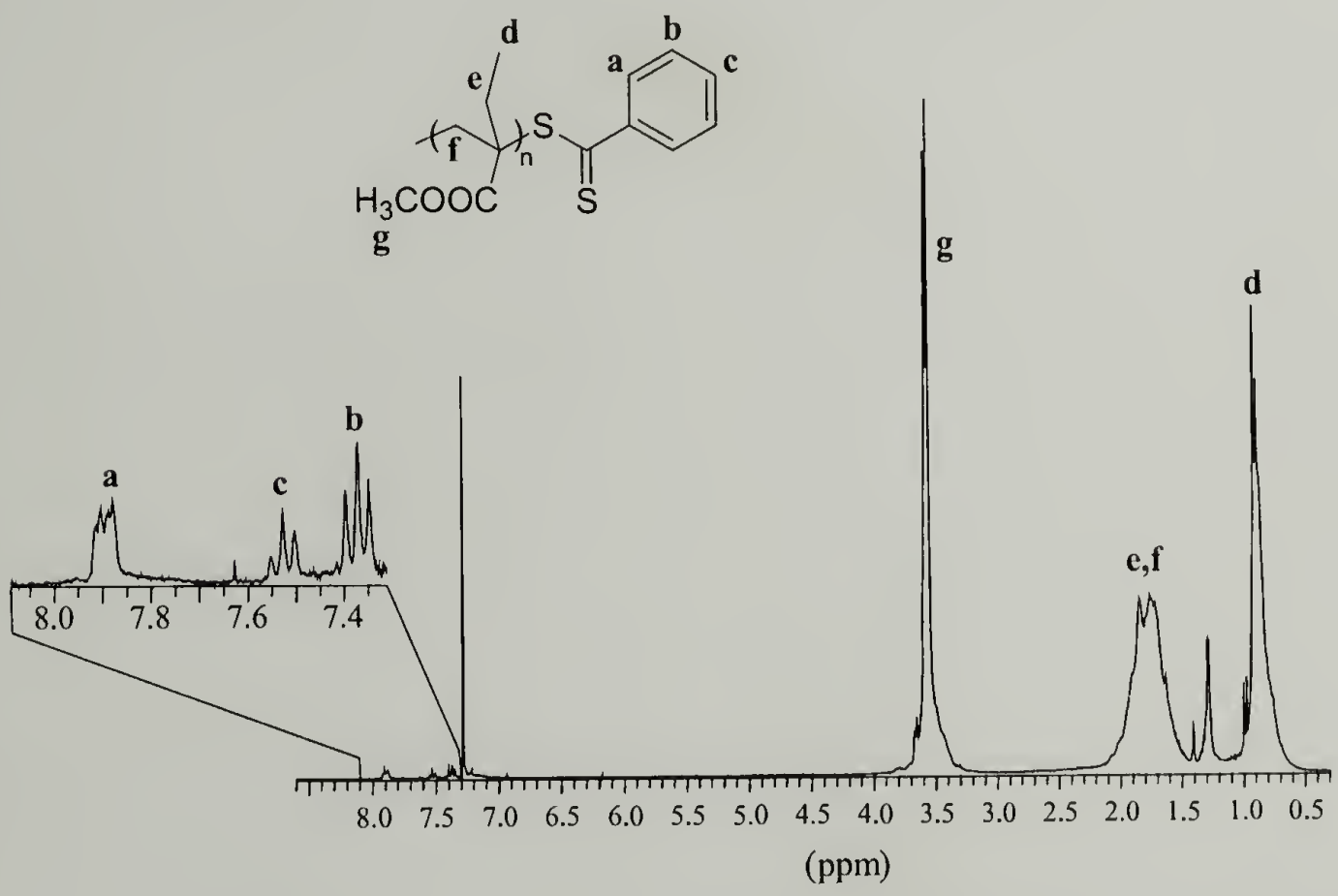


Figure 7.2. NMR spectrum of poly(MEA) obtained by high pressure RAFT polymerization.

End-Group Analysis. One of the key advantages of controlled polymerizations is the ability to reactivate chain-ends and synthesize complex polymer architectures. In a RAFT polymerization, the active chain-end is a dithioester group that can be reactivated by utilizing a free-radical initiator. The presence of dithioester end-groups was confirmed by ^{1}H NMR, with the aromatic protons clearly identified in the 7.3-8.0 ppm region (Figure 7.2). Quantification of the end-groups with NMR was difficult due to the low concentration of the end-groups in these high molecular weight polymers and the relatively high experimental error associated with NMR measurements.

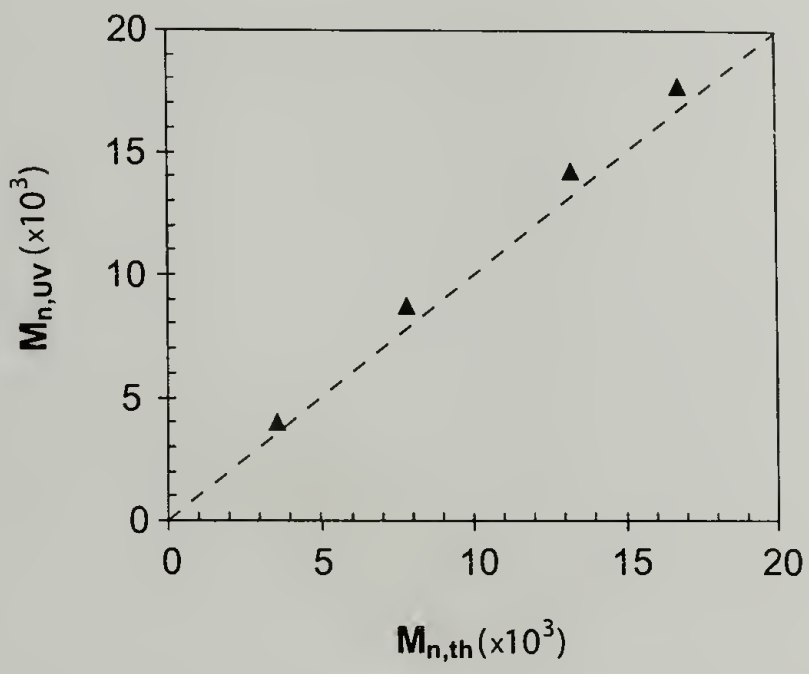


Figure 7.3. Comparison between M_n values obtained from UV measurements (assuming one dithiobenzoate end-group per chain) vs. expected M_n values (calculated from monomer-to-DTB ratios).

The dithiobenzoate group is a strong chromophore with absorbance wavelengths expanding well over 300 nm, a region where the rest of the polymer is transparent. To identify the presence of dithiobenzoate end-groups on the polymer, we conducted a GPC experiment with a UV detector set at 320 nm. Experimentally, GPC curves obtained from both refractive index (RI) and UV detectors are almost identical, confirming that the dithiobenzoate groups are indeed attached to the polymer chains. It should be noted that,

theoretically, GPC curves obtained from RI and UV detectors are not expected to be identical. RI detector measures the concentration of repeating units, while UV detector – the concentration of polymer chains. Therefore, the polymer peaks obtained from UV detector should be slightly shifted towards higher retention times. However, since molecular weight distributions of these polymers are narrow, the difference between the two curves could not be observed.

Quantitative analysis of dithioester groups was also performed using UV spectrometry. 2-Cyanoisopropyl dithiobenzoate was used as a calibration standard in order to obtain the extinction coefficient ε of dithiobenzoate groups. At a peak maximum of 304 nm in THF at 25 °C, the value of ε was measured to be 19,466 $L \cdot mol^{-1} \cdot cm^{-1}$. M_n of the polymers were calculated from the UV data assuming one end-group per polymer chain. Perfect agreement was observed between the expected M_n values and those obtained from UV measurements (Figure 7.3), confirming the presence of dithiobenzoate end-groups on almost every chain.

The polymer end-groups were also analyzed by mass spectrometric techniques (MALDI-TOF MS and ESI MS),[15-17] which allowed direct observation of a dithioester end-group on a RAFT polymer. Low molecular weight polymer was synthesized for this purpose ($M_n = 2.2 \times 10^3$, $M_w/M_n = 1.12$). The MALDI-TOF spectrum of the poly(MEA) is shown in Figure 7.4a. Each peak corresponds to a single polymeric chain with a certain number of repeating units plus a sodium cation. A single major distribution is observed, with the difference between the peaks corresponding to 114 mass units, which is the molecular mass of the repeating unit. Molar mass of the end-groups can be obtained by

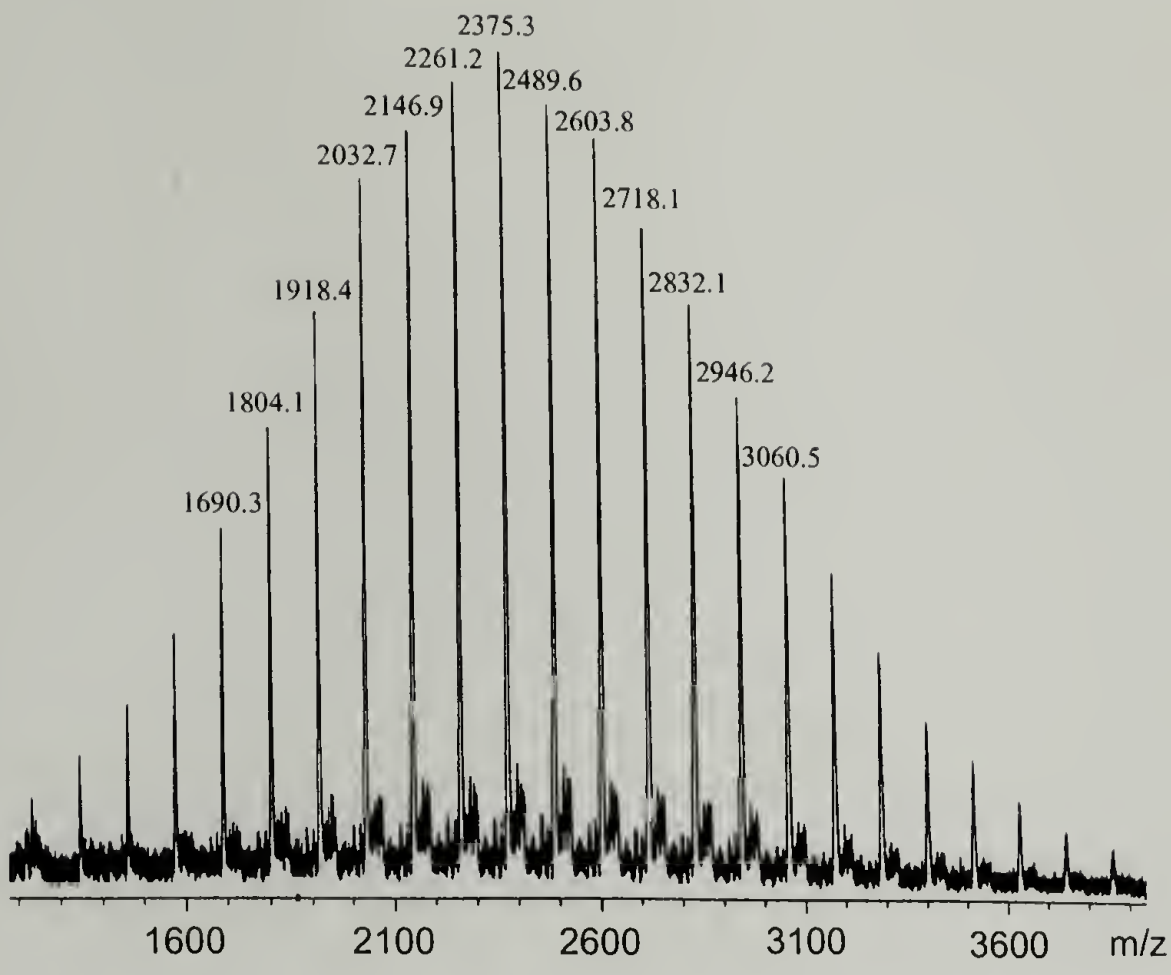
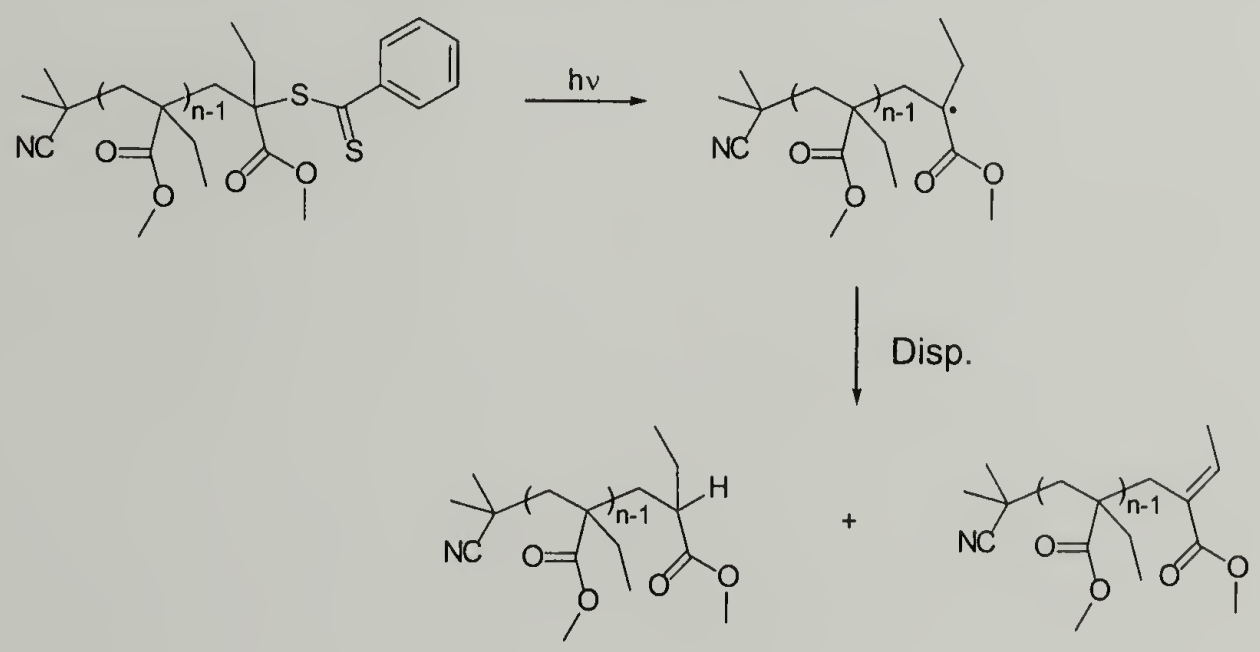


Figure 7.4. MALDI-TOF (a) and ESI MS (b, ionized by • Na^+ and ▲K^+) spectra of poly(MEA) synthesized by high pressure RAFT polymerization.

the following formula: Mass (end-group) = Mass (peak) – Mass (repeat unit)*n – Mass (cation), where n is the number of reperating units. Analysis reveals that the main peak distribution corresponds to a disproportionated polymer, i.e. polymer with either a hydrogen end-group or a double bond-containing unit. Since the difference between these two distributions is only 2 m/z units, they can only be distinguished by a careful analysis of isotopic distribution of the peaks, which was impossible in our case due to the low resolution of the spectrum. A few other low intensity distributions could be distinguished, one of which might be corresponding to the expected dithioester end-capped polymer. However, poor signal-to-noise ratio for these distributions did not allow proper assignment. On the other hand, a spectrum obtained by ESI MS shows a single distribution of peaks corresponding to the dithiobenzoate-containing end-groups (Figure 7.4b). Two distributions observed in the ESI spectrum correspond to the same polymer chains ionized with different cations, sodium and potassium.

Scheme 7.4 Photocleavage of the dithiobenzoate groups during MALDI analysis.



The difficulty in obtaining a good MALDI spectrum might be related to the fact that dithioester groups are photolabile.[18] In particular, UV laser used to achieve ionization in

MALDI can reasonably be expected to effectively cleave the group at C-S bond, generating polymeric radicals which could further undergo disproportionation (Scheme 7.4). In this case, the appearance of peaks corresponding to a disproportionated polymer in a MALDI-TOF spectrum does not necessarily indicate chain-terminating event during the RAFT polymerization. ESI MS uses much softer ionization procedure and thus allows direct observation of sensitive dithioester end-groups. It should be noted, however, that dithiobenzoate end-groups have been previously observed by MALDI MS on a poly(N-isopropylacrylamide) synthesized by RAFT.[19] A second distribution corresponding to a disproportionated polymer was also observed in this case.

Synthesis of Block Copolymers. A poly(MEA-b-styrene) diblock copolymer can be obtained from a poly(MEA) precursor by polymerizing styrene at ambient pressure and 60 °C using AIBN as the initiator (Scheme 7.5). Kinetic data and molecular weight data for the block copolymers are presented in Table 7.2.

Table 7.2. Polymerization of styrene initiated by poly(MEA)-dithiobenzoate.

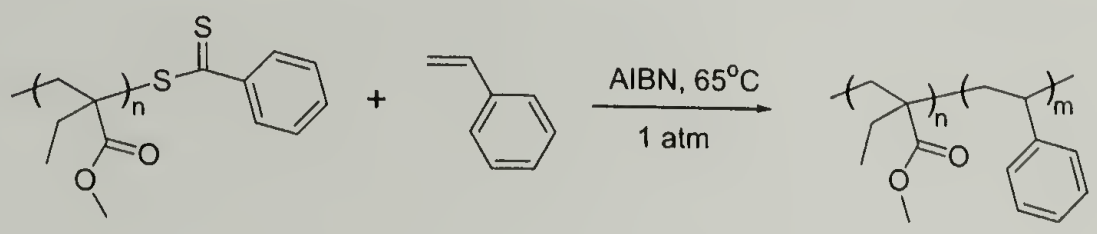
Poly(MEA) $M_n(\times10^3)$	T (°C)	[AIBN] $(\times10^{-3})$	Time (h)	Conv. (%)	M_n[a] $(\times10^3)$	M_w/M_n[a]
14.0	60	1.47	32	33	33.1 (37.4)[b]	1.22 (1.12)[b]
26.9	110	-	16.5	43	68.2 (84.4)[b]	1.23 (1.11)[b]

[a] Obtained from GPC (THF) calibrated with PS standards.
[b] After soxhlet extractions with acetonitrile and cyclohexane.

Shown in Figure 7.5, are the GPC traces for both the starting homo- and final co-polymers. High re-initiation efficiency can be inferred from the comparison between the two traces. The final copolymer peak has small shoulders in both the high and low molecular weight regions. The former results from the recombination of polystyrene

radicals and has been observed previously during the RAFT homo-polymerizations of styrene.[9] The shoulder in the lower molecular weight region can possibly arise from either some homopolystyrene, dead poly(MEA) chains, or both. It can be effectively removed by selective solvent extractions with cyclohexane and acetonitrile.

Scheme 7.5 Synthesis of block copolymers from poly(MEA)-dithiobenzoate.



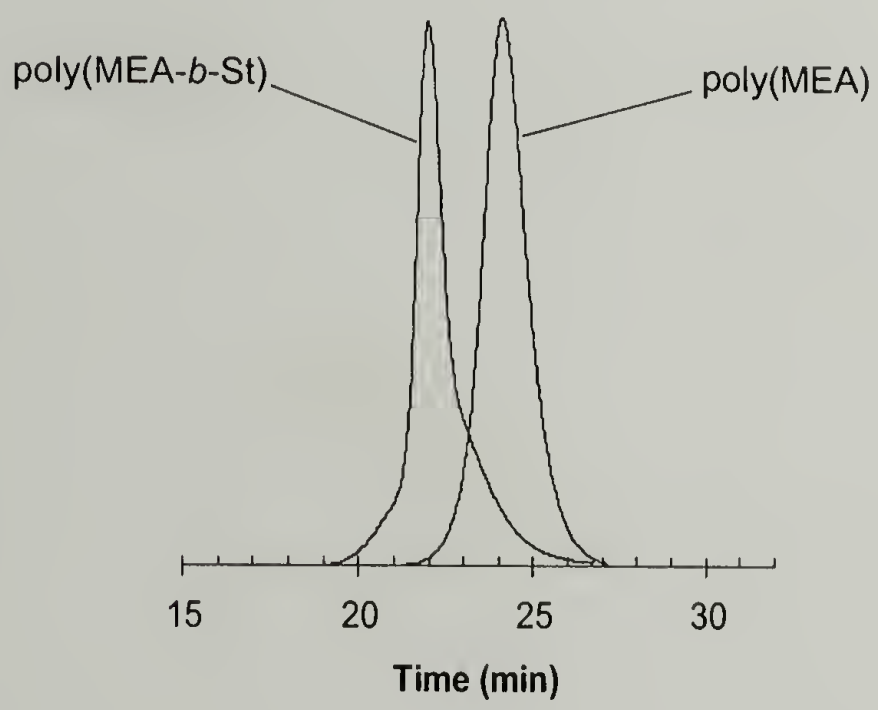


Figure 7.5. GPC traces of starting poly(MEA) ($M_n = 1.4\times10^4$, M_w/M_n = 1.17) and poly(MEA-*b*-St) ($M_n = 3.3\times10^4$, $M_w/M_n = 1.22$).

To investigate whether some unzipping of the poly(MEA) chain had occurred before the addition of the first styrene unit, a ^{1}H NMR of the crude reaction mixture was obtained before full conversion was reached. No peaks corresponding to the MEA monomer could be observed, indicating that the depropagation of poly(MEA) radical is slow enough compared to the addition on styrene and clean re-initiation had indeed

occurred. The structure of the block copolymers was also confirmed by ^{1}H NMR, with peaks similar to those observed in polystyrene and poly(MEA) spectra.

Conclusions

In conclusion, the RAFT polymerization of a sterically hindered "non-polymerizable" monomer, MEA, has been achieved under high pressure conditions, extending the pool of monomers available for living free-radical polymerization techniques. Well-controlled polymers with narrow polydispersities have been obtained. Analysis by UV and ESI MS confirmed the presence of dithioester end-groups. Poly(MEA-b-styrene) diblock copolymer were obtained by efficient re-initiation of styrene polymerization from poly(MEA) chains at ambient pressure.

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CHAPTER 8

SYNTHESIS OF WELL-DEFINED POLY(ETHACRYLIC ACID) BY HIGH-PRESSURE RAFT POLYMERIZATION

Introduction

Poly(α-alkylacrylic aeids) arc an important elass of amphiphilic polymers that have been invcstigatcd for their pH-dependcnt ability to disrupt biological mcmbranes. They havc bcen shown in particular to undergo a conformational transition as a funetion of the pH, from a hydrophobie eompaet globule in acidie environments to an cxpanded eoil at higher pHs (scc Chapter 5 for more details).[1-4] This ehangc in conformation has been eorrelated to the polymer's lytie and cytotoxie aetivities, and more directly to their ability to sclcctively disrupt biologieal mcmbranes at or close to physiological pH.[5-7] This unique behavior of poly(α-alkylacrylic acids) made them potentially useful as pH-rcsponsivc membrane disrupting agents for facilitating endosomal release of therapcutics.[8-13]

Poly(α-alkylacrylie acids) ean only bc obtained by free-radical polymerization of the corrcsponding acids.[14,15] In closc analogy to thcir ester countcrparts thc polymerizability of these α-alkylacrylic acid monomcrs bccomes very low when thc alkyl group is larger than a methyl, duc to both thermodynamic (decrease in ceiling temperature) and kinetie (slower propagation) factors. Thc low polymerizability of these monomers, in turn, prcvcnts thc use of traditional living/controlled free-radical polymcrization (LRP) tcehniques dcspite thc fact that well-dcfined poly(alpha-alkylacrylic acid)s are very much desircd for biomedical and pharmaceutical research (to understand thc

influence of molecular weights on the physico-chemical interactions with membrane, biodistribution, in vitro and in vivo cytotoxicity ... and to obtain bio-conjugates). The need for a non-traditional living/controlled polymerization approach to these synthetic targets is exacerbated by the fact that they cannot be obtained by alternate, traditional living polymerization techniques such as anionic or GTP polymerizations. The only attempt thus far to (indirectly) control the polymerization of ethacrylic acid was reported by Kim *et al.*, with some limited success in using the living anionic polymerization of protected ester monomers to obtain well-defined polymers.[16]

In this chapter, we present some preliminary results on the high-pressure reversible addition-fragmentation chain-transfer (HP-RAFT) polymerization of ethacrylic acid and its derivatives. In Chapter 5, we had shown that high pressure can be used to dramatically improve the polymerizabilities of α-alkylacrylic acids. Here, we apply a LRP protocol under similar conditions to polymerize ethacrylic acid precursors and obtain well-defined poly(ethacrylic acid) with low polydispersities, controlled molecular weights, and defined end-groups.

Experimental Section

Materials. All chemicals were purchased from Aldrich Chemical Co. 2,2'-azobis(isobutyronitrile) (AIBN) was recrystallized from methanol, all other chemicals were used without further purifications. Ethacrylic acid (**1**),[17] *tert*-butyl ethacrylate (**2**),[16] benzyl ethacrylate (**3**),[16] and 2-cyanoisopropyl dithiobenzoate[18] were synthesized according to previously published procedures.

Synthesis of 2-(trimethylsilyl)ethyl ethacrylate (**4**). Triethylamine (4.9 mL, 35 mmol) was added dropwise to a solution of **1** (3.5 ml, 35 mmol) in CH_2Cl_2 (15.0 mL) maintained

at 0 °C. DCC (8.3 g, 40 mmol) and DMAP (0.5 g, 4 mmol) were added to the reaction mixture. 2-(trimethylsilyl)ethanol (5.0 mL, 35 mmol) was then added dropwise at 0 °C for 30 min. The mixture was stirred at room temperature for 19 hours. The obtained solid was removed by filtration. The remaining mixture was subjected to column chromatography (petroleum ether : EtOAc 9:1 (v:v)), providing pure **4** in 29 % yield. ^{1}H NMR ($CDCl_3$, TMS, δ, ppm): 0.05 (s, 9H), 1.04 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H), 2.32 (q, J = 7.4 Hz, 2H), 4.25 (m, 2H), 5.51 (s, 1H), 6.12 (s, 1H).

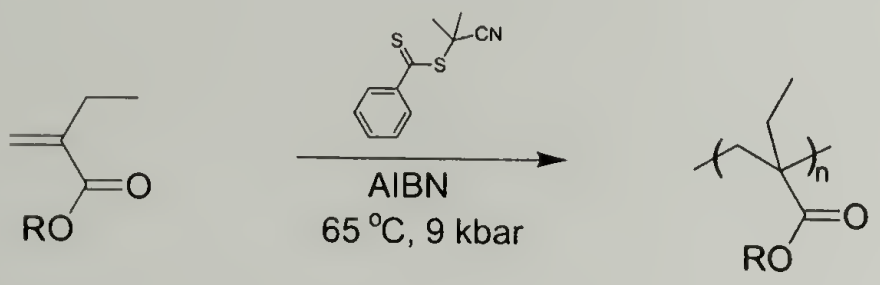
Polymer Synthesis. All polymerizations were carried out in 2 mL Teflon ampules in a high-pressure reactor purchased from the High Pressure Research Center of the Polish Academy of Sciences. The equipment included a model LCP20 hydraulic press and a pressure reaction vessel equipped with a temperature controller. The monomers used in these experiments were deoxygenated by bubbling with nitrogen for 10-15 minutes prior to polymerization. The polymers were precipitated in a non-solvent (ether for poly(**1**), methanol for the others) and dried *in vacuo*. Yields were determined gravimetrically.

Deprotection of poly(**4**). To a solution of the polymer (0.1 g) in 0.5 mL of DMF was added 1.0 mL of tetrabutylammonium fluoride solution (1 mol·L^{-1} in THF). The mixture was stirred overnight at 60 °C and under nitrogen. The solvent was evaporated, and the mixture acidified by adding a few drops of concentrated HCl. The final polymer was precipitated in acidic water (pH = 3), filtered, and dried. Conversions were determined by NMR (> 95%).

Measurements. Molecular weights of the polymers were determined by gel permeation chromatography (GPC) with a Waters 510 HPLC pump, Waters R400 Differential Refractometer detector, and three PLgel columns (5 μm, 1x 50 Å and 2x

MIXED-D). The system was calibrated with narrow poly(methyl methacrylate) (PMMA) standards. NMR analysis was performed on a Bruker DPX 300 spectrometer, operating at 300.15 MHz (^{1}H).

Scheme 8.1 RAFT polymerization of ethacrylic acid and its derivatives.



Acrylate	R
1	–H
2	$-C(CH_3)_3$
3	$-CH_2-C_6H_5$
4	$-CH_2-CH_2-Si(CH_3)_3$

Results and Discussion

An unmodified RAFT polymerization of the unprotected ethacrylic acid **1** was attempted as the most direct route to a well-defined poly(ethacrylic acid) (Scheme 8.1). The polymerization of **1** in DMF at 9 kbar and 65 °C, in the presence of 2-cyanoisopropyl dithiobenzoate (DTB) as the RAFT reagent and AIBN as a free-radical initiator, resulted in very slow polymerization (Table 8.1). In addition, the polymerization was much slower than expected based on the results previously obtained for the corresponding methyl ester monomer and already presented in Chapter 7, indicating that some strong retardation of unknown origin was taking place under these RAFT conditions. This observation was rather curious as it had already been established that RAFT polymerizations are compatible with a carboxylic acidic functionality and, in particular, that the RAFT polymerization of a monomer such as acrylic acid proceeds in a well-controlled manner at ambient pressure.[19-21] It is tempting, based on these facts, to attribute the peculiar observations made here to a combination of several parameters that include the simultaneous use of high pressures, RAFT chemistry and an acidic

functionality. In particular, it can be hypothesized that hydrogen bonding between carboxylic groups on two polymeric chains in the polymeric RAFT adduct provides a compact structure with leads to a large volume change and therefore large activation volume for fragmentation of this adduct. This in turn results in a large decrease in the rate of fragmentation with pressure, providing significant retardation. Since it had been shown by results reported in Chapter 7 that the polymerization of ethacrylic esters can be well controlled by high pressure RAFT, we turned our attention to the polymerization of ethacrylic acid derivatives where the acidic group is protected by easily removable functionalities.

Table 8.1. RAFT polymerization of ethacrylic acid and its derivatives under high pressure conditions.[a]

Acrylate	Time (h)	Conv. (%)	$M_{n,th}$[b] ($\times 10^3$)	M_n[c] ($\times 10^3$)	M_w/M_n[c]
1	29	5	0.5	-	-
2	30	13	4.1	3.3	1.80
3	5	47	17.9	9.5 (17.8)[d]	1.17
3	9	73	27.8	19.7	1.15
4	12	84	11.8	15.2	1.19
4	15	90	27.0	31.0	1.17

[a] $P = 9$ kbar, $T = 65$ °C, 50% v/v in MEK (DMF for **1**).
[b] Calculated from acrylate-to-RAFT reagent ratio.
[c] Obtained from GPC (THF) relative to PMMA standards.
[d] Obtained from UV assuming one dithiobenzoate end-group per chain.

The HP-RAFT polymerization of the *tert*-butyl-protected ethacrylic acid **2** (Scheme 8.1) was slow, and provided polymers with high polydispersities (Table 8.1). In addition, the GPC trace of the obtained polymer showed a bimodal distribution. To test whether the bulky *tert*-butyl group was responsible for the low polymerization rate, the same monomer was polymerized at high pressure in the absence of the RAFT reagent

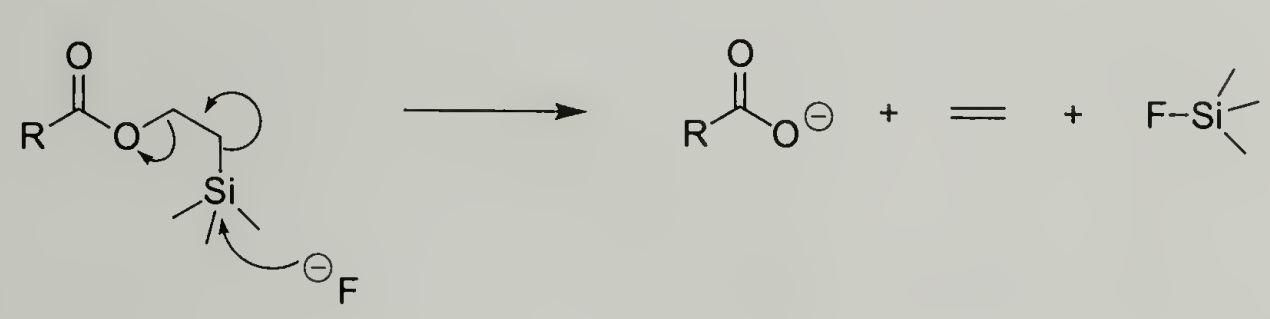
('uncontrolled' conditions). The polymerization proceeded at a fast rate (18% yield after 60 min) at 5 kbar and 65 °C with 2 mol-% of AIBN. Both the polymerization rate and molecular weight of the polymer (GPC (PMMA standards): $M_n = 3.0\times10^4$, $M_w/M_n = 1.8$) were comparable to the values previously observed for methyl ethacrylate, suggesting that the size of the *tert*-butyl group does not decrease the free-radical polymerizability of the acrylate to a large extent and cannot account for the observed slow polymerization of **2** under HP-RAFT conditions. While the exact reason for the loss in control at high pressure is not clear yet, it is obvious that this indirect methodology based on a *tert*-butyl protecting group is not suitable for the preparation of well-defined poly(ethacrylic acid).

In contrast to the above results, the HP-RAFT polymerization of the benzyl-protected ethacrylate monomer **3** (Scheme 8.1) proceeded rapidly, and resulted in low polydispersity polymers (Table 8.1). The relative molecular weights of poly(**3**) obtained from GPC according to a PMMA calibration were significantly lower than expected based on theory, but M_n values obtained from UV measurements (see Chapter 7 for further details on the technique) – assuming one dithiobenzoate end-group per polymer chain – correlated well with the expected values. Since the molecular weights obtained from end-group analysis represent absolute values, it can be easily concluded that the deviation observed between the GPC M_n and the expected M_n values derives from the different solvation properties of poly(**3**) and PMMA under the chromatographic conditions used for the analysis.

Attempts to remove the benzyl groups of poly(**3**) by catalytic hydrogenolysis and convert it to the polyacid poly(**1**) were unsuccessful. No decrease in the intensity of the benzyl proton peaks could be observed by NMR when hydrogen gas and a Pd/charcoal

catalyst were used, even after prolonged reaction times and using freshly obtained catalyst. Hydrogenolysis with Pd/charcoal catalyst under otherwise identical conditions has been reported to be effective in deprotecting poly(benzyl methacrylate) synthesized by group-transfer polymerization,[22] while it was also shown that the nature of the catalytic system, in terms of structure and morphology, can have a dramatic influence on the efficiency of the hydrogenolysis for polymers.[23] We suspect that the lack of activity observed for our polymer results (at least partly) from the presence of dithiobenzoate end-groups on the polymers. It is well known that sulfur-containing derivatives can act as very effective poisons for hydrogenation catalysts,[24] and therefore might be preventing the clean debenzylation of poly(**3**).

Scheme 8.2 Deprotection of 2-(trimethylsilyl)ethyl group.

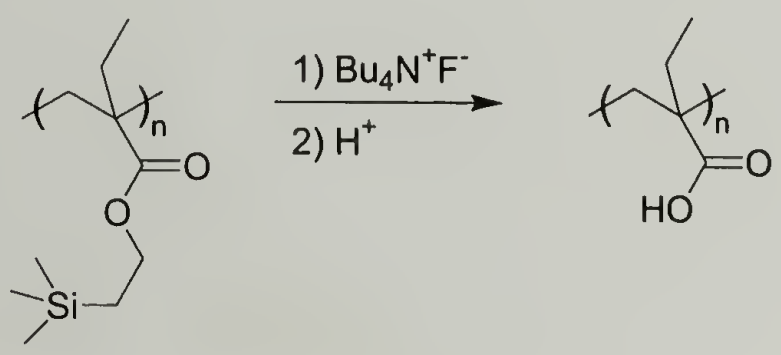


In a final (and successful) attempt to reach our goal of synthesizing poly(**1**), a 2-(trimethylsilyl)ethyl group (TMSE) was explored as an alternate protecting group for ethacrylic acid. This silicon-containing protecting group can be easily cleaved by reaction with fluoride reagents, via a mechanism involving the direct attack of the fluoride on the silicon and the subsequent release of ethylene and trimethylsilyl fluoride (Scheme 8.2). Although being regularly used in the synthesis of small organic molecules,[25] TMSE had not been employed for the preparation of acid-containing polymers when we started the project. While we were conducting our own experiments,

Jones *et al.* independently reported the use of TMSE as a protecting group for polyacrylic and polymethacrylic acids obtained by atom-transfer radical polymerization.[26]

The TMSE-protected ethacrylic acid **4** (Scheme 8.1) polymerized at high rate under high-pressure RAFT conditions, and provided polymers with narrow molecular weight distributions. The molecular weights of the polymers obtained by GPC were close to the expected values calculated from the 'monomer-to-RAFT reagent' ratios. The presence of dithiobenzoate end-groups in poly(**4**) could be observed by GPC with the UV detector set at 320 nm, a wavelength at which only the dithiobenzoate functionalities absorb.

Scheme 8.3 Deprotection of TMSE protected poly(ethacrylic acid).



The deprotection of poly(**4**) was carried out with tetrabutylammonium fluoride in a THF/DMF mixture (Scheme 8.3). The reaction was followed by monitoring the disappearance of the TMSE peaks in the ^{1}H-NMR spectrum. A maximum conversion of 50% could initially be reached at room temperature. When the temperature was increased to 60 °C, a complete deprotection of the TMSE groups was achieved. A comparison of the ^{1}H-NMR spectra of the starting poly(**4**) and of poly(**1**), the deprotected polymer is available in Figure 8.1. Note the complete disappearance of peaks **d**, **e** and **f** corresponding to the protons present on the TMSE group.

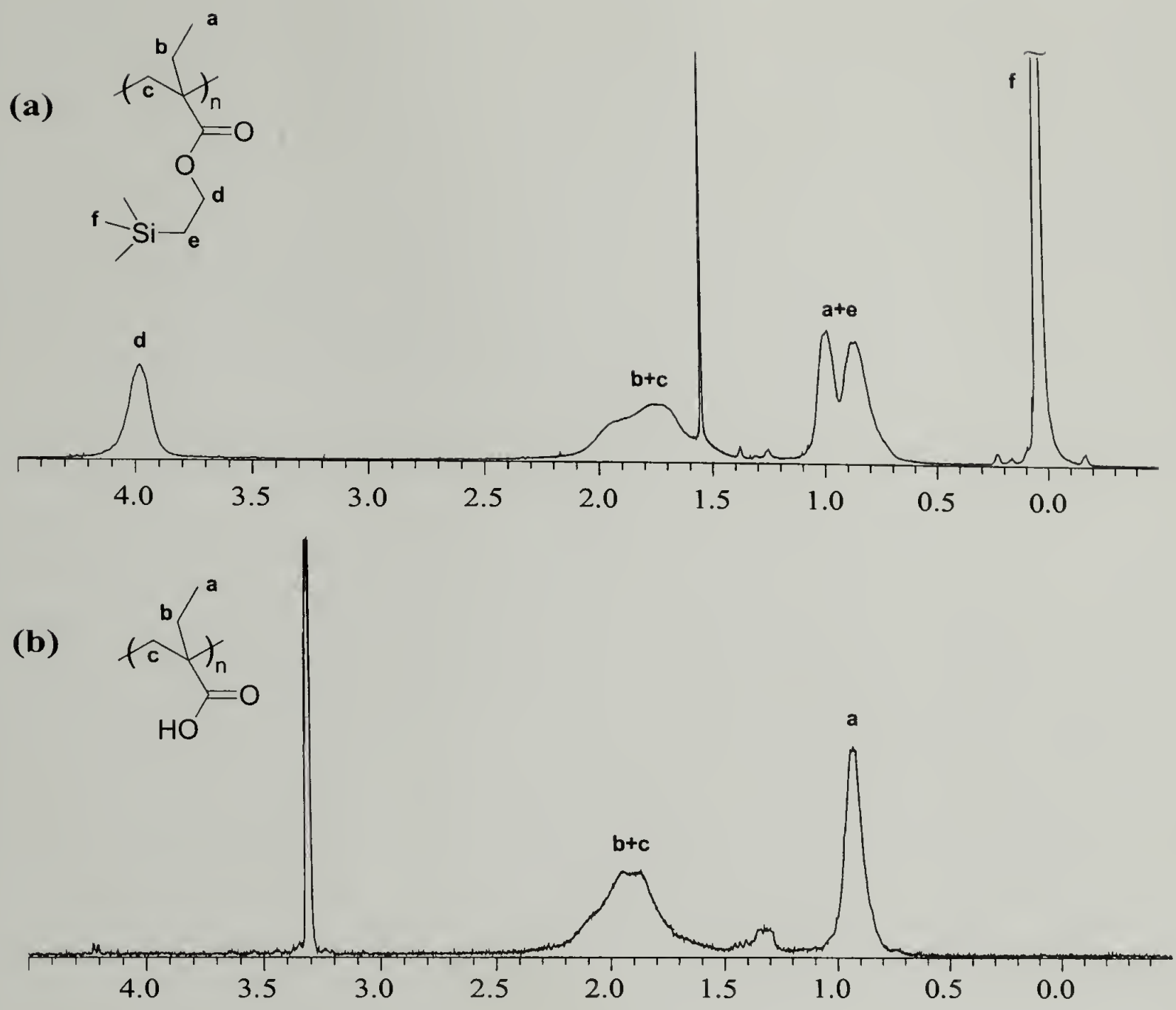


Figure 8.1. NMR spectra of (a) poly(**4**) in $CDCl_3$, and (b) the completely deprotected poly(ethacrylic acid) in d_3-MeOH.

Conclusions

The direct HP-RAFT polymerization of ethacrylic acid and of a *tert*-butyl-protected version of the same monomer resulted in very slow polymerizations. A benzyl-protected ethacrylic acid polymerized rapidly to provide well-controlled polymers, but the debenzylation reaction by catalytic hydrogenolysis could not be achieved, probably due to the catalyst being poisoned by the dithiobenzoate end-groups.

A well-defined poly(ethacrylic acid) was finally obtained by polymerization of a TMSE-protected ethacrylic acid under HP-RAFT conditions, and subsequent deprotection of the obtained polymer with tetrabutylammonium fluoride. This methodology allows for the synthesis of poly(α-alkylacrylic acid)s with low polydispersities, controlled molecular weights and end-groups. Further reduction of the dithiobenzoate end-group to a thiol, and subsequent coupling with proteins may provide an easy route to poly(α-alkylacrylic acid) bioconjugates.[27]

Acknowledgements. Gwenaelle Pound is gratefully acknowledged for conducting initial studies on the controlled polymerization of **1** and **2**.

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CHAPTER 9

SYNTHESIS OF LIVING POLYMERS OF ULTRA-HIGH MOLECULAR WEIGHTS BY A FREE-RADICAL POLYMERIZATION TECHNIQUE

Introduction

Synthetic methods based on living polymerizations are indispensable for modern polymer chemists. By minimizing the influence of termination and chain transfer over the final outcome of the polymerization, they provide the only reasonable route to polymers with narrow molecular weight distributions and controlled end-groups, and to most of the non-linear polymer architectures such as block, star, cyclic and other macromolecules with controlled branching patterns.[1-5] By making possible the design of polymers with tailored properties, they have contributed significantly to the development of nanostructured polymeric materials whose dimensions are controlled by the size of the macromolecules involved in the structuration process.[5,6]

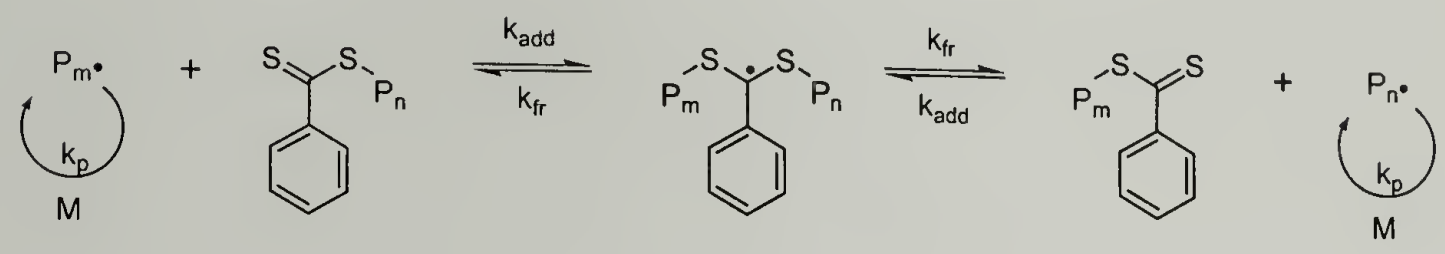
The many fundamental accomplishments and myriad of papers published every year on the synthesis, properties, and use of polymers prepared by living polymerization techniques contrast heavily with the industrial impact, which thus far has been quite modest, largely due to the high costs associated with the required reaction conditions. Living polymerizations demand that a propagation proceeds hundred of times in sequence without the interference of any side reaction leading to termination or chain transfer. Such a selectivity is hardly a hallmark of organic chemistry, and only a handful of polymerizations have been successfully optimized to the required level.[1,5]

Living/controlled free-radical polymerization techniques were supposed to overcome this technical limitation by allowing experimental conditions to be used that are less stringent and costly than those based on organometallic or ionic species, a goal that has largely been achieved by now.[7] Free-radical polymerizations have their own limitations, though. Being very slow, they do not provide a good route to polymers of high degrees of polymerization, the polymerizations in this case requiring theoretical reaction times of several weeks to several years depending on the targeted degree of polymerization.[8]

In this Chapter, we report a simple, practical methodology to overcome the above limitation. We demonstrate, using methyl methacrylate (MMA) polymerization as an example, that very high molecular weight polymers can be obtained under very simple experimental conditions that are fully compatible with current industrial polymerization processes. The methodology uses known living/controlled free-radical polymerization procedures, and overcome their inherent limitations under normal conditions by using very high hydrostatic pressures, in the 1-10 kbar range (1 kbar = 987 atm = 14,504 psi). The main purpose of using high pressures is to considerably increase the propagation rate coefficient of the polymerization[9] and make it reasonably fast, with reaction times of less than a few hours even when the amount of propagating free-radicals has to be maintained very low in order to maintain the living/controlled character of the reaction. Although theoretically expandable to most living/controlled free-radical polymerization techniques described in the literature, the present study uses RAFT conditions to control the livingness. A mechanistic scheme summarizing the key steps in a RAFT polymerization

is provided in Scheme 9.1. Further information on the scope, limitations, and mechanism of RAFT-type reactions is available in the literature.[10-13]

Scheme 9.1 Equilibrium between dormant and active species during RAFT polymerization.



Experimental Section

Materials. The RAFT agent **1** was synthesized according to a procedure reported in the literature.[11] All other chemicals were purchased from Aldrich. MMA was distilled before use and AIBN recrystallized in methanol; all other reagents were used as received.

High-Pressure Polymerizations. Polymerizations were carried out in 2 mL Teflon ampoules in a high-pressure micro-reactor purchased from the High Pressure Research Center of the Polish Academy of Sciences. The reactor includes a hydraulic press model LCP20 and a pressure reaction vessel equipped with a temperature controller. The initial solution was deoxygenated by bubbling with nitrogen for 20-30 minutes prior to polymerization. Polymers were precipitated in methanol. Yields were determined gravimetrically.

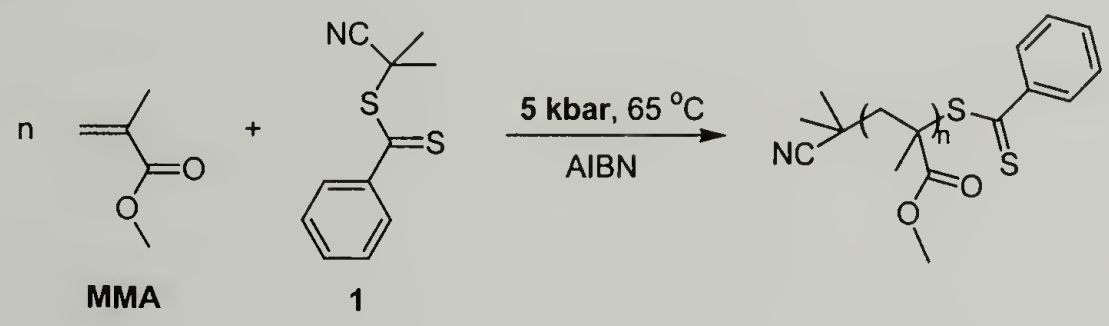
Measurements. Molecular weights of the polymers were determined by Polymer Laboratories PL-220 high temperature GPC system equipped with two PL MIXED-A columns, Wyatt MiniDawn (620 nm diode laser) light scattering detector and refractive index detector. Measurements were performed at 135 °C in 1,2,4-trichlorobenzene with a flow rate of 1.0 $ml \cdot min^{-1}$. PMMA standards of very high molecular weights were used to

estimate the influence of the second virial coefficient on the scattering signal, and recalibrate the light-scattering detectors accordingly. Polymers with medium-high molecular weights (< 300,000) were characterized by GPC in THF using 13 monodisperse PMMA commercial standards as calibrants (2×MIXED-D and 1×50 Å columns, 25 °C, 1.0 $ml \cdot min^{-1}$). ^1H NMR spectra were recorded on a 300 MHz Bruker DPX 300 spectrometer.

Results and Discusion

In all experiments, MMA was polymerized in a high-pressure reactor at 5 or 9 kbar and at 65°C in the presence of cyanoisopropyl dithiobenzoate (**1**) as the RAFT agent and 2,2'-azobis(isobutyronitrile) (AIBN, **2**) as the free-radical initiator (Scheme 9.2). Although bulk polymerization is possible, solvents such as toluene and methyl ethyl ketone (MEK) were used to avert very high viscosities. Polymers were characterized by GPC coupled to a multi-angle laser light-scattering (MALLS) detection unit to prevent problems associated with instrumental broadening.

Scheme 9.2 High-pressure RAFT polymerization of MMA.



The NMR spectra of the synthesized PMMA indicated that the polymers have 72% syndiotactic dyads, close to the tacticity obtained by free-radical polymerization at

ambient pressure. This observation is consistent with previous reports that indicated a very small dependence of PMMA tacticity on polymerization pressures.[14]

As shown in Table 9.1, polymers of very high molecular weights (up to 1.25 million) and very low polydispersities ($M_w/M_n < 1.2$, see also Figure 9.1) can be obtained after reasonably short reaction times (< 9 h). The highest molecular weight of 1.25 million does not correspond to an upper limit, but to our inability to reliably measure the molecular weight distributions of PMMA samples of higher molecular weight based on the equipment currently available to us.

Table 9.1. RAFT polymerization of MMA under high-pressure conditions.[a]

Exp.	Solvent	$[M]_o:[1]_o:[2]_o$	Time (h)	Conv. (%)	$M_{n,th}$[b] ($\times 10^{-3}$)	$M_{n,GPC}$[c] ($\times 10^{-3}$)	M_w/M_n[c]
1	MEK	2,000:1:0.1	2	61	122	114[d]	1.15[d]
2	MEK	2,000:1:0.1	5	>99	200	202	1.04
						197[d]	1.15[d]
3[e]	MEK	2,000:1:0.1	2	>99	200	150[d]	1.61[d]
4	MEK	5,000:1:0.1	9	>99	500	485	1.03
5	Toluene	1,000:1:0.1	2.5	89	89	87[d]	1.07[d]
6	Toluene	12,000:1:0.2	1	9	108	164	1.20
7	Toluene	12,000:1:0.2	2	30	360	367	1.03
8	Toluene	12,000:1:0.2	4	72	864	838	1.05
9	Toluene	12,000:1:0.2	7	>99	1,200	1,250	1.03

[a] $P = 5$ kbar, $T = 65$ °C, [MMA] = 4.67 M.
[b] Calculated from the monomer-to-1 ratio.
[c] Measured by GPC-MALLS.
[d] Measured by GPC relative to PMMA standards.
[e] $P = 9$ kbar.

The degrees of polymerization reported in this communication are the highest ever obtained for a living free-radical polymerization leading to a linear polymer. Results for living/controlled free-radical polymerizations published in the literature have consistently led to a practical upper limit of about 2×10^3 for the degree of polymerization.[7,15,16]

From a preparative viewpoint, it is interesting to note that the polymerization can be driven to completion without loss of control over the molecular weights.

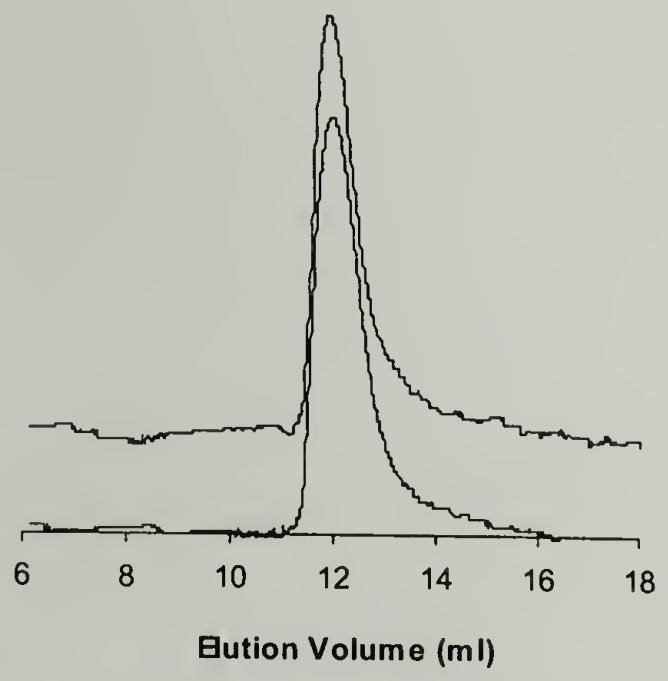


Figure 9.1. GPC chromatograms of a commercial PMMA standard (top curve, M_n = 1.3×10^6 g·mol^{-1}, PDI = 1.03) and a PMMA sample synthesized in this study by HP-RAFT polymerization (bottom curve, $M_n = 1.25\times10^6$ g·mol^{-1}, PDI = 1.03).

The observed linear increase in molecular weight and decrease in polydispersities with conversion (Figure 9.2) are consistent with a living/controlled mechanism. An analysis of the kinetic data reveals that the polymerization does not follow the expected first order kinetics with respect to monomer concentration over the entire conversion range. The rate of polymerization increases significantly with increasing conversion (Figure 9.3), a behavior probably related to a progressive viscosity buildup in the reactor. In a free-radical polymerization, including RAFT, the concentration of free-radicals is governed by a steady-state kinetic equilibrium, i.e. the difference between their production rate (decomposition of the initiator) and their consumption rate (termination). The increase in viscosity slows down the rate of diffusion-controlled termination and therefore leads to an increase in the free-radical concentration and the overall rate of

polymerization. This autoacceleration behavior, although unusual for a controlled process, is nevertheless highly beneficial from a preparative standpoint as high molecular weight polymers can be obtained in much shorter times than expected based on strict first-order kinetics. Extrapolation of the initial kinetic features to higher conversions shows that 49 hours would have been necessary to reach 99 % conversion while the polymerization was actually complete in only 7 hours.

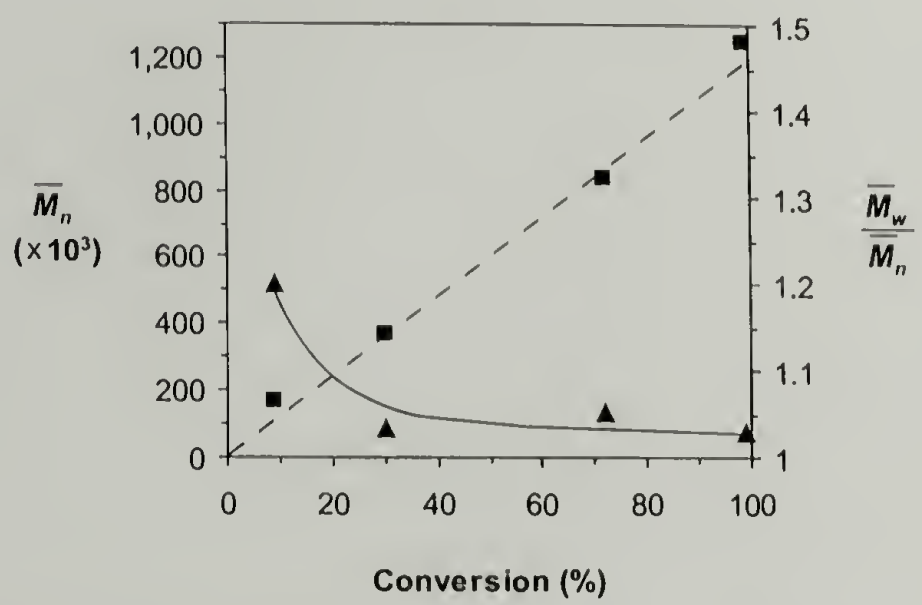


Figure 9.2. Dependence of molecular weights (■ $M_{n,GPC}$; ---theoretical curve) and polydispersities (▲) on conversion for RAFT polymerization of MMA at 5 kbar (T = 65 °C, [MMA] = 4.67 M in toluene, [MMA]:[**1**]:[**2**] = 12,000:1:0.2).

The polymerizations were carried out in the presence of inert diluents (50 vol-%) in order to provide enough mobility to the reactive polymer chains up to high conversions. Excellent results were obtained with either methyl ethyl ketone (MEK) and toluene when medium-high molecular weights were targeted ($< 0.5\times10^6$). When higher molecular weights were needed and very low amounts of the RAFT agent and initiator had to be used, toluene provided far better results (Entries 6-9 in Table 9.1). This is probably due to some impurities present in MEK at low concentrations, such as peroxides, since MMA was found to polymerize in regularly purified MEK even in the absence of any added

AIBN, while no such polymerization could be observed when MEK was passed through an alumina column to remove peroxidic impurities.

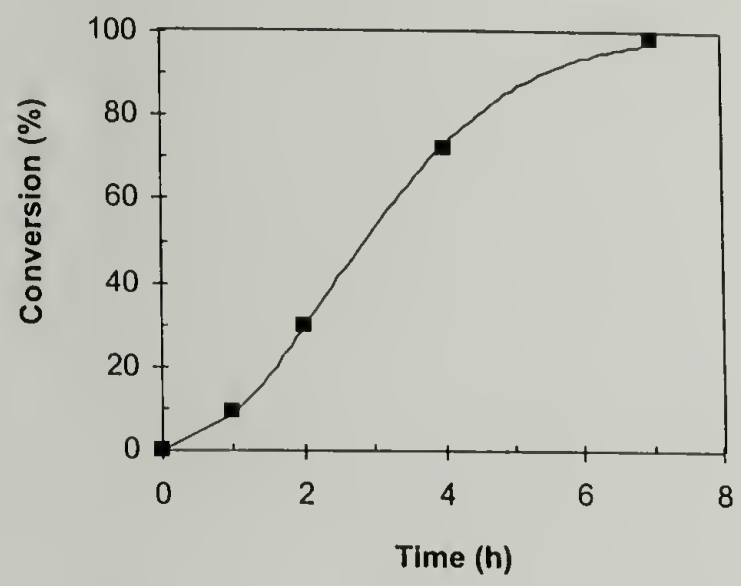


Figure 9.3. Evolution of monomer conversion with time for RAFT polymerization of MMA at 5 kbar (T = 65 °C, [MMA] = 4.67 M in toluene, [MMA]:[**1**]:[**2**] = 12,000:1:0.2).

Dithiobenzoate end-groups of medium-high molecular weight polymers could be observed by GPC coupled to UV detector set at a wavelength of 320 nm, a region where the rest of the polymer is transparent. GPC analysis of the crude polymerization mixture is shown in Figure 9.4. Polymer peaks obtained by RI and UV detection appear at the same retention volume and no other peaks are present in the UV trace, indicating that a clean initiation is taking place and all the dithiobenzoate groups are attached to the polymer chains. The dithiobenzoate end-groups can also be reactivated in the presence of a free-radical initiator and used for the synthesis of diblock copolymers (see Chapter 10). It should noted that due to the presence of dithioester end-groups, the polymers have slightly pinkish color. Transformation of the end-groups by reduction to thiols can be used as an effective way to decolorize and end-functionalize the polymers (see Appendix).

The exact influence of several parameters on HP-RAFT polymerizations is currently under investigation, but it is already clear that using higher pressures is not always helpful. As an example, polymerization at 9 instead of 5 kbar (Entry 3 in Table 9.1) resulted in a higher polydispersity index. The origin of this effect is unclear and might result from a decreased chain transfer constant to the RAFT agent or from the fact the gel point is reached, but these and other findings[17] clearly suggest that experimental conditions have to be carefully optimized and that simple extrapolation based on conditions reported for ambient pressure polymerization is not feasible.

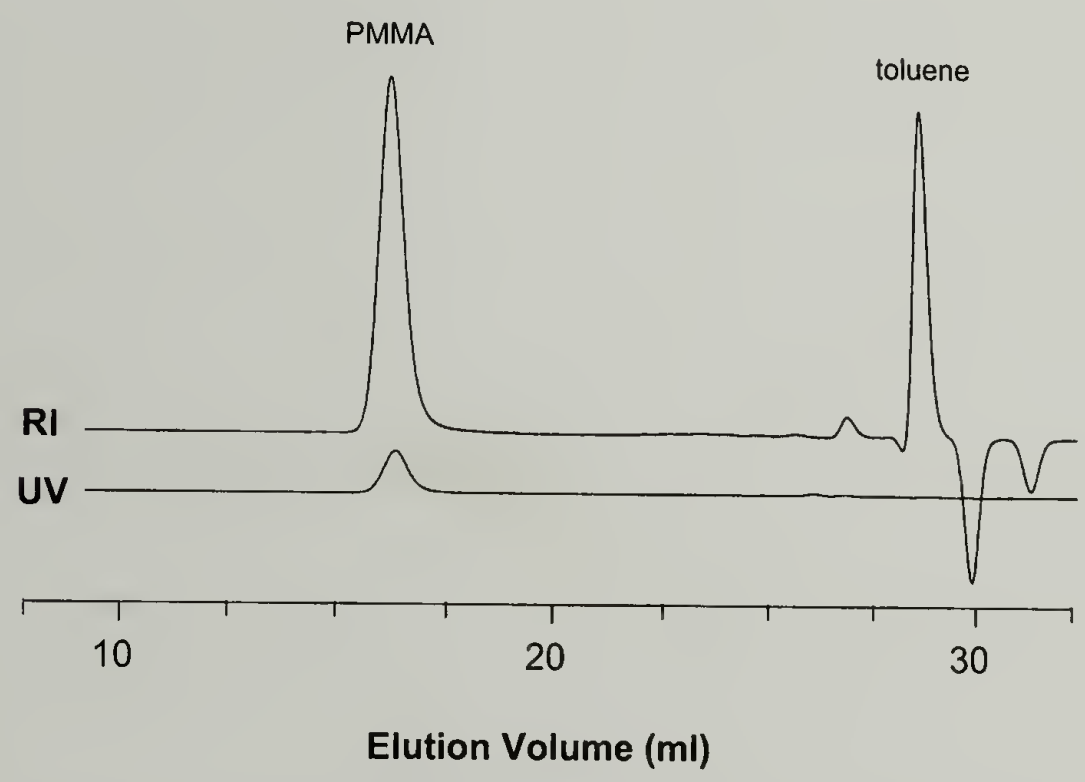


Figure 9.4. GPC traces of PMMA obtained by HP-RAFT polymerization (Entry 5 in Table 9.1) *before* precipitation (top curve – RI detector; bottom curve – UV detector).

The reactors needed to obtain the high pressures reported in this study are rarely found in research laboratories, but are easy to access in industry. In addition, recent progress in food science where multi-liters high-pressure reactors of the type used in this study are currently used to eliminate bacteria from food according to the high-pressure

equivalent of pasteurization, should increasingly make the purchase of such pieces of equipment attractive to synthetic chemists.[18,19]

Conclusions

In summary, we have demonstrated that vinyl polymers of extremely high molecular weights can be easily obtained using living/controlled free-radical polymerization techniques at high pressures. This HP-RAFT and associated techniques should allow the entire range of molecular weights to become accessible for most vinyl polymers, and provide an easy route to advanced polymeric materials whose ultimate properties (optical, mechanical, porosity, etc.) critically depends upon the molecular weight of at least one component.[20-22]

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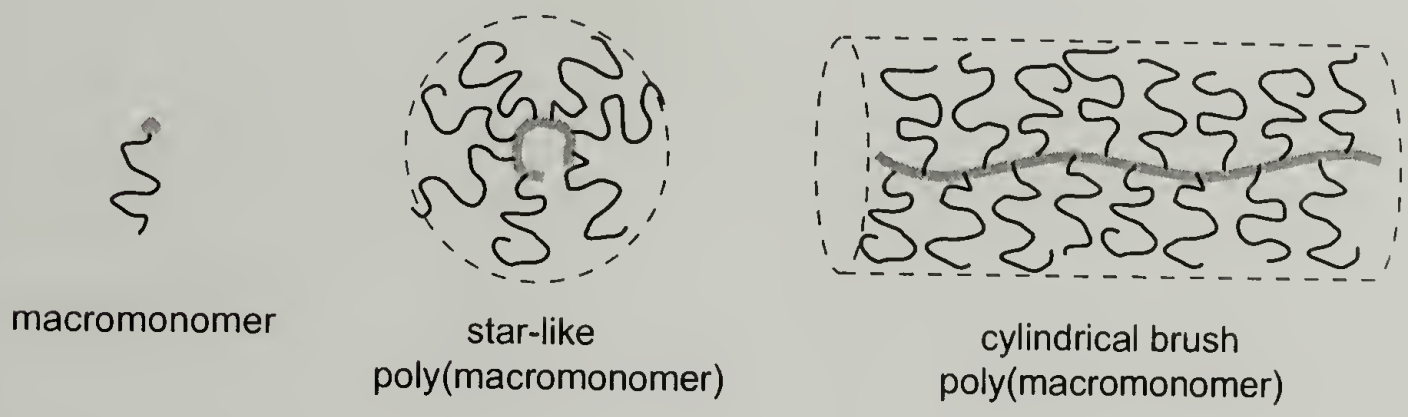
CHAPTER 10

CONTROLLED SYNTHESIS OF POLY(MACROMONOMERS) BY HIGH-PRESSURE RAFT POLYMERIZATION

Introduction

Poly(macromonomers) are densely branched polymers possessing a comblike architecture. They display the highest possible branching density along the main backbone, with a polymer chain attached to each repeating unit. Depending on the chemical nature and degree of polymerization of the backbone and side-chains, poly(macromonomers) adopt different conformations, ranging from star-like spheres to elongated cylinders (Scheme 10.1).[1-5]

Scheme 10.1 Poly(macromonomer)s.



When the polymeric branches are longer than the main backbone, the polymer resembles a multiarm star. In contrast, when the length of the main backbone is sufficiently large, the steric crowding of the pendant polymeric chains in the resulting comb forces the main backbone to adopt an extended conformation, leading to a rigid cylindrical shape for the molecule. The persistent shape of these poly(macromonomers)

and the possibility of dimensional control by changing the length of the pendant polymer chains and the main backbone make these macromolecules potentially useful as building blocks in the construction of nanoscopic supramacromolecular assemblies and devices. Poly(macromonomers) can be prepared either by a direct polymerization of the corresponding macromonomers or by various grafting techniques. Despite the bulky nature of the macromonomers and low propagation rate coefficients (k_p), their free-radical polymerization under classical conditions can lead to high degrees of polymerization as a result of very low termination rate coefficients (k_t), which put the overall polymerizability $k_p k_t^{-1/2}$ in an acceptable range.[6-8] A number of different poly(macromonomers) and random copoly(macromonomers) of high degrees of polymerization, but broad molecular weight distributions, have been synthesized by this approach.[9-12]

A living polymerization of these monomers is more difficult. The low k_p values limit the usefulness of classical living free-radical or anionic protocols, although some limited success has been observed in particular cases.[13,14] A "grafting from" approach can be used to obtain low polydispersity poly(macromonomer)s by subsequent controlled polymerization of the backbone and side chains.[15-19] This approach is not as flexible as the first one, however. It does not guarantee that each repeating unit in the backbone is substituted, and does not allow the easy synthesis of more complicated structures such as random or block copoly(macromonomers).

In this Chapter, we describe our attempts to achieve the living/controlled polymerization of polystyrene macromonomers by high pressure RAFT (HP-RAFT). High pressures are used in these experiments as a kinetic driving force to increase the k_p

of macromonomers and allow their controlled free-radical polymerization. The synthesis of linear-comb diblock copolymers is also described.

Experimental Section

Materials. 2-Cyanoisopropyl dithiobenzoate (DTB) was synthesized as described previously.[20] AIBN was recrystallized from methanol. Benzene was distilled from purple sodium-benzophenone ketyl, while styrene was dried over calcium hydride and distilled under vacuum before use.

Synthesis of Polystyrene Macromonomers. An anionic polymerization was carried out using standard Schlenk techniques under dry nitrogen atmosphere. Dry benzene (50 mL) and styrene (5 mL, 4.4×10^{-2} moles) were charged into a heat-dried, nitrogen-purged 100 mL flask. A few drops of *sec*-butyllithium (sBuLi, 1.4 mol·L^{-1} in cyclohexane) were added to the mixture until the light red color remained constant. 1.25 mL of sBuLi (1.75×10^{-3} moles) were added into the flask, the solution becoming dark red in color. The polymerization was allowed to proceed for 3 hours at room temperature with constant stirring. Ethylene oxide was bubbled through the mixture until the red color completely disappeared (3 min), and 1.7 mL of methacryloyl chloride (1.74×10^{-2} moles) was charged into the flask. The mixture was stirred at room temperature for 16 hours, and the polymer precipitated in excess methanol. A GPC analysis (PS standards) provided the following molecular weight characteristics for the macromonomer: M_n = 2.4×10^3 and $M_w/M_n = 1.09$.

High-Pressure Polymerizations. Polymerizations were carried out in 2 mL Teflon ampoules in a high-pressure reactor purchased from the High Pressure Research Center of the Polish Academy of Sciences. The equipment included a hydraulic press model

LCP20 and a pressure reaction vessel equipped with a temperature controller. The reagents were depleted of oxygen by bubbling with nitrogen, and transferred into the Teflon ampoules under nitrogen atmosphere. The polymers were precipitated in methanol, and dried *in vacuo*. The conversion of the macromonomer to the polymer was followed by GPC.

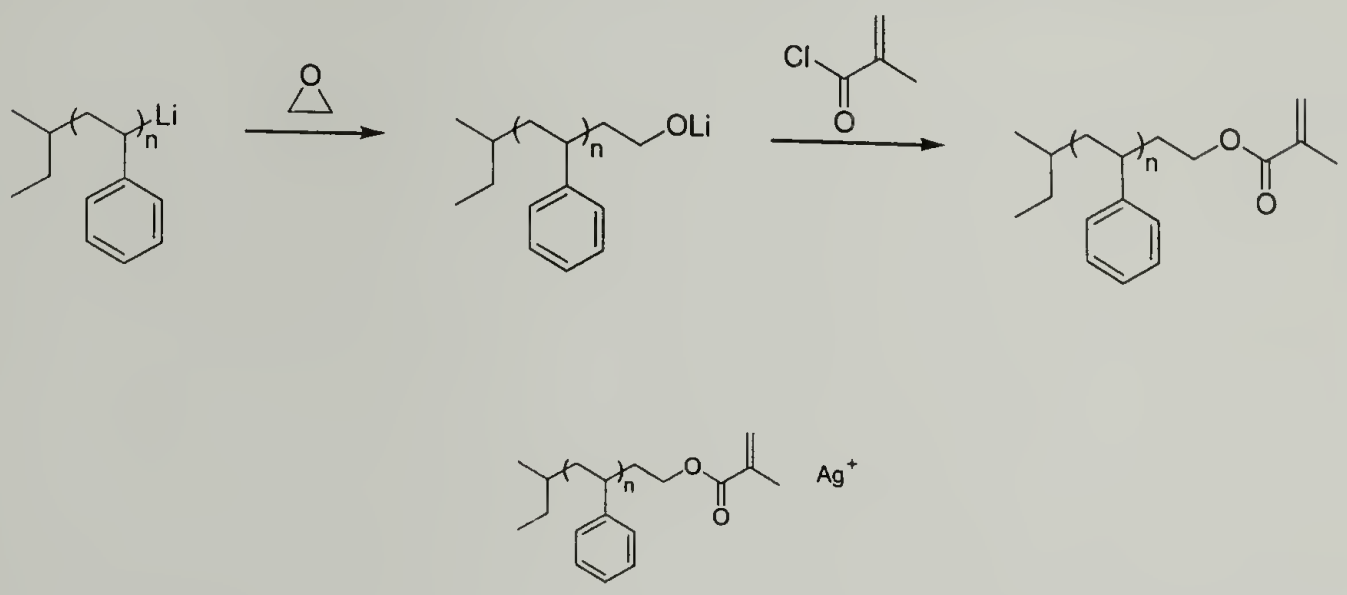
Measurements. The molecular weights of the polymers were determined by gel permeation chromatography (GPC) with a Waters 510 HPLC pump, Waters R400 differential refractometer, and three PLgel columns (5 μm, 1x 50 Å and 2x MIXED-D). The system was calibrated with narrow polystyrene standards. NMR analysis were performed on a Bruker DPX 300 spectrometer, operating at 300.15 MHz (^{1}H). MALDI-TOF spectra were recorded on a Bruker REFLEX III mass spectrometer. Dithranol was used as the matrix and silver triflouroacetate as the external cation source.

Results and Discussion

Synthesis of Macromonomers. Polystyrene-methacrylate macromonomers (PS-MA) were conveniently synthesized by anionic polymerization in a one-pot procedure from the literature.[21] Living polystyryl anions were reacted with ethylene oxide and subsequently quenched with methacryloyl chrolide (Scheme 10.2). Ethylene oxide end-capping has been shown to result in monoaddition if carried out in the presence of Li counterions.[22,23] In a subsequent step, a tenfold excess of methacryloyl chloride was used to quantitatively quench the oxide end-capped polystyrene. Precipitation of the forming LiCl started as soon as the reagents were mixed, although the reaction was allowed to proceed for 16 hours to ensure completion. ^{1}H NMR was used to confirm the presence of the methacrylate end-groups on the polymers. In addition, the MALTI-TOF spectrum of

the macromonomers showed a single distribution of peaks corresponding to the expected methacrylate end-capped structure (Figure 10.1).

Scheme 10.2 Synthesis of methacrylate end-capped polystyrene.



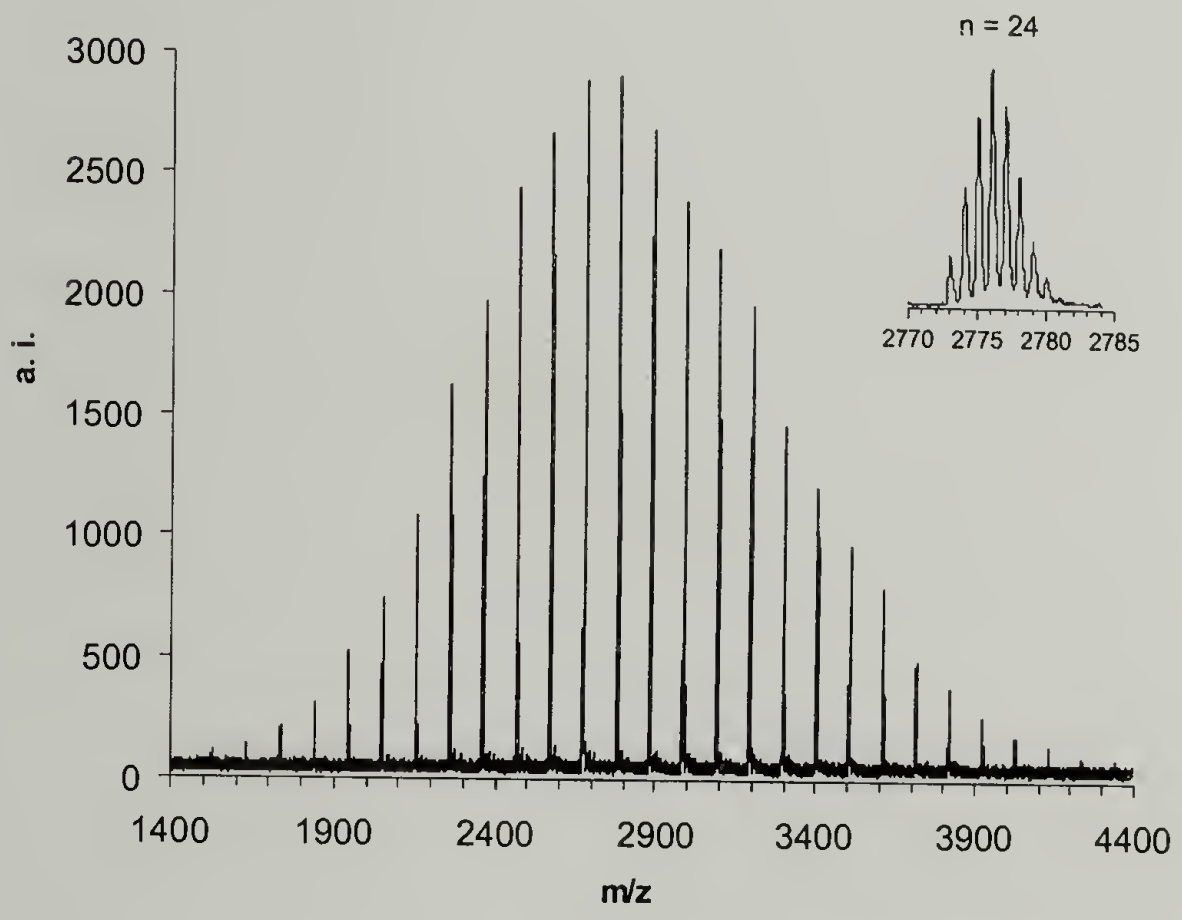
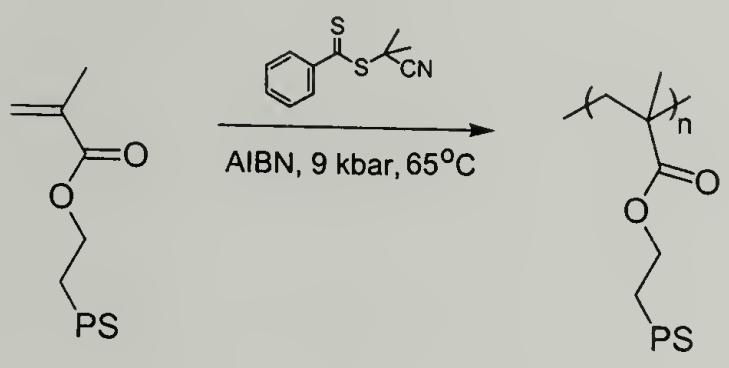


Figure 10.1. MALDI-TOF spectrum of the polystyrene-methacrylate macromonomer prepared by anionic polymerization.

HP-RAFT Polymerization of PS-MA Macromonomer. PS-MA was polymerized in toluene solutions at 9 kbar in the presence of DTB as the RAFT reagent and AIBN as

the free-radical initiator (Scheme 10.3). A GPC chromatogram of the polymerization mixture is shown in Figure 10.2. Peaks corresponding to a starting PS-MA as well as to a forming poly(PS-MA) are clearly distinguishable, and can be used to estimate the conversion.

Scheme 10.3 RAFT polymerization of PS-MA.



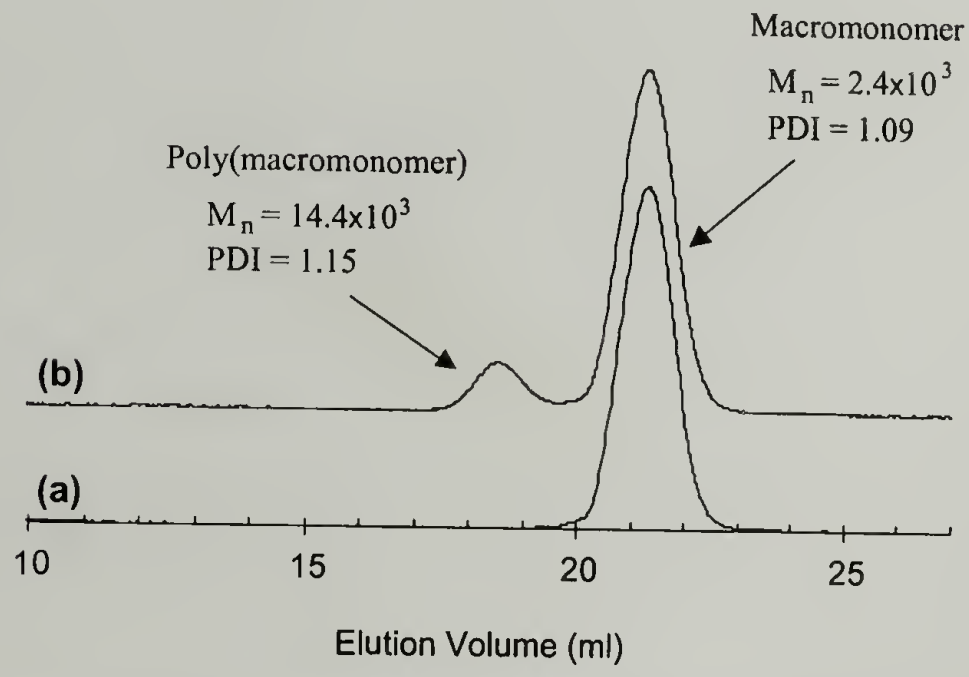


Figure 10.2. GPC chromatograms of the starting macromonomer (a) and polymerization mixture (b).

Polymerizations conducted at 65 °C resulted in polymacromonomers of low polydispersity (Table 10.1). The molecular weights of the obtained poly(PS-MA) were found to increase with conversion, although M_n values obtained from GPC relative to linear polystyrene standards were much lower than predicted by theory. This deviation is expected, and can be attributed to the highly branched structure of the obtained poly(PS-

MA). Branched polymers have lower hydrodynamic volumes compared to their linear analogs, and their molecular weights are overestimated by classical GPC techniques using linear polymer as calibrants.[24,25]

The polymerization of PS-MA was quite slow even at 9 kbar with reaction times in the order of several days. The observed slow polymerization is not only due to the steric crowding and slower propagation but also due to the lower concentration of reactive double bonds in the reactive medium. When the concentration effect is taken into account and the appropriate correction factor is used, the polymerizability of PS-MA macromonmers becomes similar to what was observed previously for methyl methacrylate at 5 kbar. Polymerizations were conducted at the highest accessible concentration that could ensure the formation of a homogeneous liquid phase for the starting reactive medium (polymacromonomer, initiator, RAFT agent, and solvent). Increasing the polymerization temperature to 90 °C resulted in a much faster rate, but led to polymers of broader molecular weight distribution (PDI of 1.62) as determined by GPC (Table 10.1).

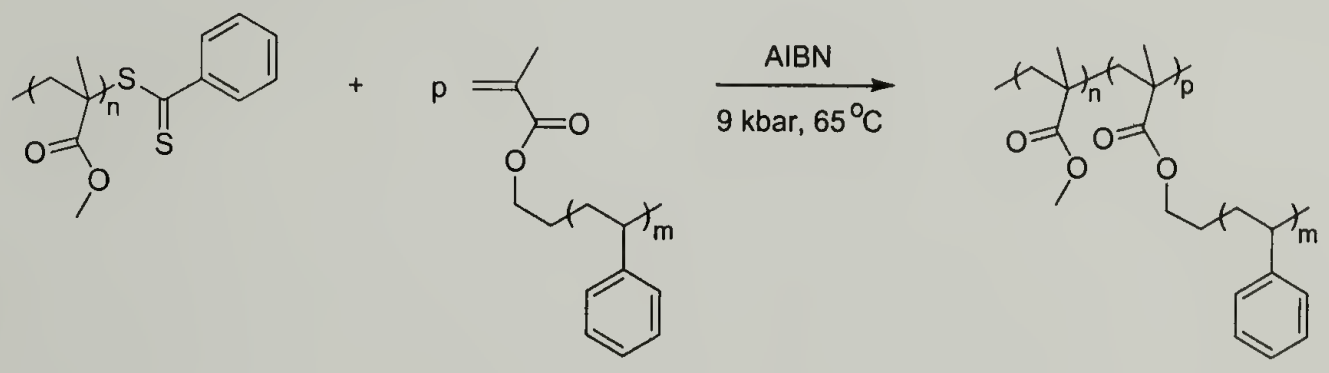
Table 10.1. High-pressure RAFT polymerization of PS-MA.[a]

RAFT reagent	*T* (°C)	Time (h)	Conv. (%)	$M_{n,th}$[b] ($\times 10^3$)	M_n[c] ($\times 10^3$)	M_w/M_n[c]
DTB	65	20	14	33.6	14.4	1.15
DTB	65	40	26	62.4	24.3	1.22
DTB	90	23	34	81.6	41.2	1.62
PMMA-DTB[d]	65	60	78	273.8[e]	141.8[f] (196.6)[g]	1.15[f]

[a] P = 9 kbar, PS-MA ($M_n = 2.4\times10^3$) = 1 g, toluene = 1 mL, [DTB]:[AIBN] = 10:1. [b] Calculated from macromonomer-to-RAFT reagent ratio. [c] Obtained from GPC relative to linear PS standards. [d] PMMA-DTB ($M_n = 86.6\times10^3$, $M_w/M_n = 1.07$), PS-MA = 1 g, toluene = 2.5 mL, [PMMA-DTB]:[AIBN] = 2.5:1. [e] Molecular weight of the diblock copolymer. [f] Obtained from GPC after extraction with cyclohexane. [g] Calculated from NMR data.

Synthesis of Block Copolymers Based on Poly(PS-MA). The polymerization of PS-MA can also theoretically be initiated from a polymeric RAFT reagent to yield diblock copolymers with adjoining linear and branched blocks. To test this hypothesis, a poly(methyl methacrylate) (PMMA-DTB) sample obtained by HP-RAFT polymerization (Chapter 9, Entry 5 in Table 9.1, $M_n = 8.7\times10^4$, $M_w/M_n = 1.07$) was used as a macro-RAFT reagent (Scheme 10.4). The polymerization was carried out in toluene at 9 kbar and 65 °C. Compared to polymerizations conducted in the presence of DTB, more toluene had to be used to co-solubilize the reactive partners. To compensate for the lower concentration of double bonds resulting from the use of a macromonomer, more AIBN was used, obtaining a ratio of about 40 mol-% compared to the dithiobenzoate groups. Since the amount of dead polymer chains is related to the concentration of free-radical initiator in the medium, such a high amount of AIBN is not acceptable for traditional RAFT polymerizations. However, due to a much slower decomposition of AIBN at high pressures[26] coupled to lower rates of termination,[27,28] much higher concentrations of AIBN can be tolerated in HP-RAFT processes.

Scheme 10.4 Synthesis of a (linear PMMA)-(brush PS) block copolymer.



GPC chromatograms of the initial mixture and of the obtained diblock copolymer are shown in Figure 10.3 (**a** and **b**, respectively). Conversions were estimated from the GPC trace obtained under UV detection at 254 nm, a wavelength where only polystyrene

segments can absorb. The peak corresponding to the copolymer has a shoulder at higher elution volumes (lower molecular weights or, more precisely, lower polymer sizes), extending even further than the starting PMMA peak. Since it would be rather unusual that the size of the obtained copolymer in solution is lower than the size of the starting polymer, the shoulder results most probably from the homopolymerization of PS-MA initiated by AIBN radicals.

Since the shoulder contains polymers that contain polystyrene segments exclusively, it can be expected that the impurity can be easily removed, together with the unreacted PS-MA, by selective extraction with cyclohexane as the diblock copolymer containing PMMA block does not dissolve in that solvent. GPC chromatograms of the extracted fraction and the purified (continuous Soxhlet extraction for 6 hours) copolymer are shown in Figure 10.3 (**c** and **d**, respectively). The diblock copolymer has a narrow molecular weight distribution ($M_w/M_n = 1.15$), indicating that fast and complete initiation from PMMA-DTB had occurred. The ratio between PS and PMMA blocks calculated from ^{1}H NMR analysis was found to be 55:45. Knowing the molecular weight of the starting PMMA, the M_n of the final diblock can be calculated to be 1.97×10^5, with the PS-MA block of $M_n = 1.10 \times 10^5$ and $X_n = 46$ (degree of polymerization of the backbone). The GPC-based molecular weight of the diblock copolymer (based on a calibration with linear polystyrene standards) is significantly lower than the absolute M_n obtained from NMR, which is expected for a branched polymer. However, the M_n calculated from NMR is also lower than the expected (theoretical) value of 2.74×10^5. This deviation can be explained by the fact that theoretical M_n values for RAFT polymerizations are normally calculated from the monomer-to-RAFT reagent ratios without taking into

account the amount of chains directly initiated by AIBN radicals. Due to the high concentration of AIBN used in this study, the contribution of AIBN-initiated chains is not negligible anymore. Therefore, the deviation between experimental and theoretical molecular weights is not an indication of some side reactions taking place, but results from a 'normal' overestimation of the theoretical M_n values.

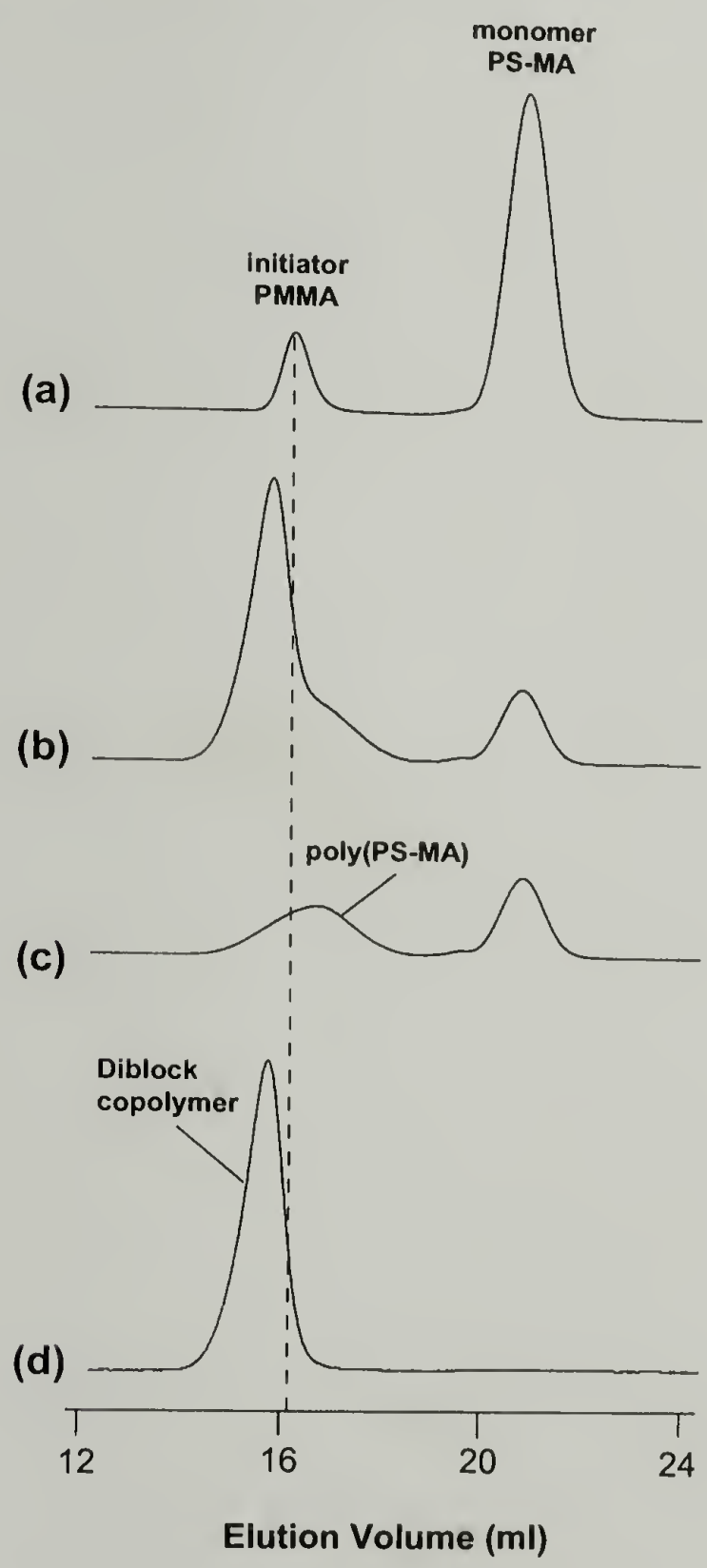


Figure 10.3. GPC analysis (RI traces) of PS-MA polymerization initiated by PMMA-DTB: (a) initial polymerization mixture, (b) final polymerization mixture, (c) fraction extracted by cyclohexane, (d) fraction insoluble in cyclohexane – diblock copolymer.

Poly(PS-MA) homopolymers resulting from the direct initiation by AIBN-generated free radicals have a M_n of 6.3×10^4 and a broad molecular weight distribution (M_w/M_n = 1.52). The high polydispersities compared to those observed for the diblock copolymer result from the slow rate of initiation. While the initiation of PS-MA chains from PMMA radicals occurs rapidly as a part of the addition-fragmentation equilibrium, AIBN initiation is a slow process taking place continuously throughout the polymerization. It is interesting to note that a diblock copolymer of narrow molecular weight distribution can be obtained under these RAFT conditions despite the high amount of AIBN used. As was discussed earlier, the rate of radical termination is significantly reduced at high pressures, which allows to maintain the "living" character of these polymerizations even at relatively high concentrations in free-radical.

Conclusions

The high pressure RAFT polymerization of polystyrene macromonomers was studied as a route towards well-defined macromolecular nanoobjects of cylindrical and spherical shapes. Polymerization conducted at 9 kbar and 65 °C resulted in low-polydispersity polymeric brushes. Molecular weights (GPC) were found to increase with conversion, yet were consistently lower than the expected values, probably due to the highly branched nature of the polymeric backbone.

The polymerization of PS-MA in the presence of PMMA-DTB as a macro-RAFT reagent provided a well-defined diblock copolymer of linear PMMA and brush-PS. Unreacted PS-MA as well as AIBN-initiated poly(PS-MA) homopolymer were easily removed by selective solvent extraction with cyclohexane.

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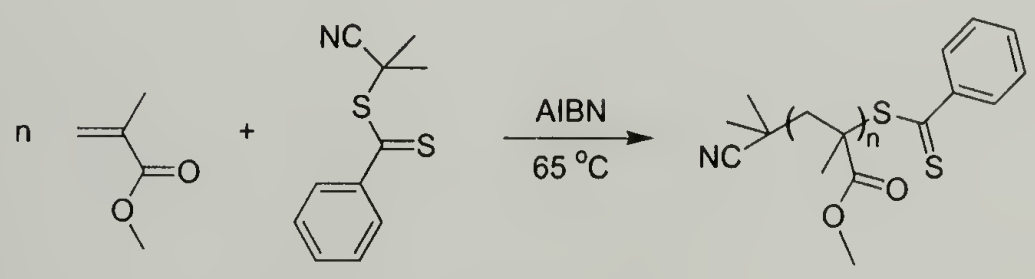
APPENDIX

MALDI-TOF MASS SPECTROMETRIC ANALYSIS OF END-GROUP TRANSFORMATION IN PMMA OBTAINED BY RAFT POLYMERIZATION

The end-functionalization of polymers is an important tool for the synthesis of tailored materials. Polymers synthesized by RAFT polymerization contain dithioester end-groups that can be used for the end-functionalization or the synthesis of more complex polymeric architectures such as diblock copolymers.[1-4] In this appendix, we describe a detailed MALDI-TOF analysis of the transformation of dithiobenzoate end-groups on poly(methyl methacrylate) (PMMA) to thiols and subsequently to thiolactones in the presence of primary amines. Conditions for the preparation of thiol end-capped PMMA are also suggested.

The PMMA samples used in this study were prepared by polymerization of MMA in the presence of cyanoisopropyl dithiobenzoate (DTB)[5] as the RAFT reagent and AIBN as free-radical initiator (Scheme A.1). The polymer sample used for this study had a M_n of 2.7×10^3 and M_w/M_n of 1.24 (polymerization conditions: 70 °C, 1 atm, bulk, [MMA]:[DTB]:[AIBN] = 100:1:0.02, time = 3 hours, conversion = 19%).

Scheme A.1 RAFT polymerization of MMA.



The MALDI-TOF spectrum of this PMMA is shown in Figure A.1. A single distribution of peaks can be observed, which at first glance may suggest the presence of a single end-group structure on each polymer chain. A closer look at the isotopic distribution of individual peaks reveals a more complex pattern than what would be expected from a single polymeric chain ionized with a sodium cation. A detailed analysis reveals that each signal in Figure A.1 is a combination of two peaks coming from PMMA chains terminated with a hydrogen and a double-bond, respectively. As suggested in Chapter 7, the presence of two end-groups on the terminal side of the polymer chain results from of a photochemical and/or thermal homolytic cleavage of dithiobenzoate end-groups induced by the laser used for ionization/desorption of the polymer chain during the MALDI-TOF experiment. This first step is followed by the disproportionation of the polymeric radicals.

Figure A.2 shows the simulation data corresponding to the isotopic distributions of polymeric Na^+ adducts with hydrogen and C=C end-groups, respectively, on an oligomer containing 19 repeating units. The end-group on the other side of the chain is assumed to be a cyanoisopropyl fragment from either the RAFT reagent or AIBN. The two distributions differ by 2 mass units and, when overlapped, result in the complex isotopic distribution pattern shown in Figure A.2c. This pattern is very similar to the pattern observed experimentally (Figure A.1). An ideal disproportionation mechanism should lead to a molar ratio of 50:50 for the two distributions. This is not observed due to the difficulty of obtaining quantitative informations by MALDI-TOF. Polymer chains with different end-groups can possibly have different ionization potentials, and the experimentally observed peak intensities do not necessarily represent the true molar

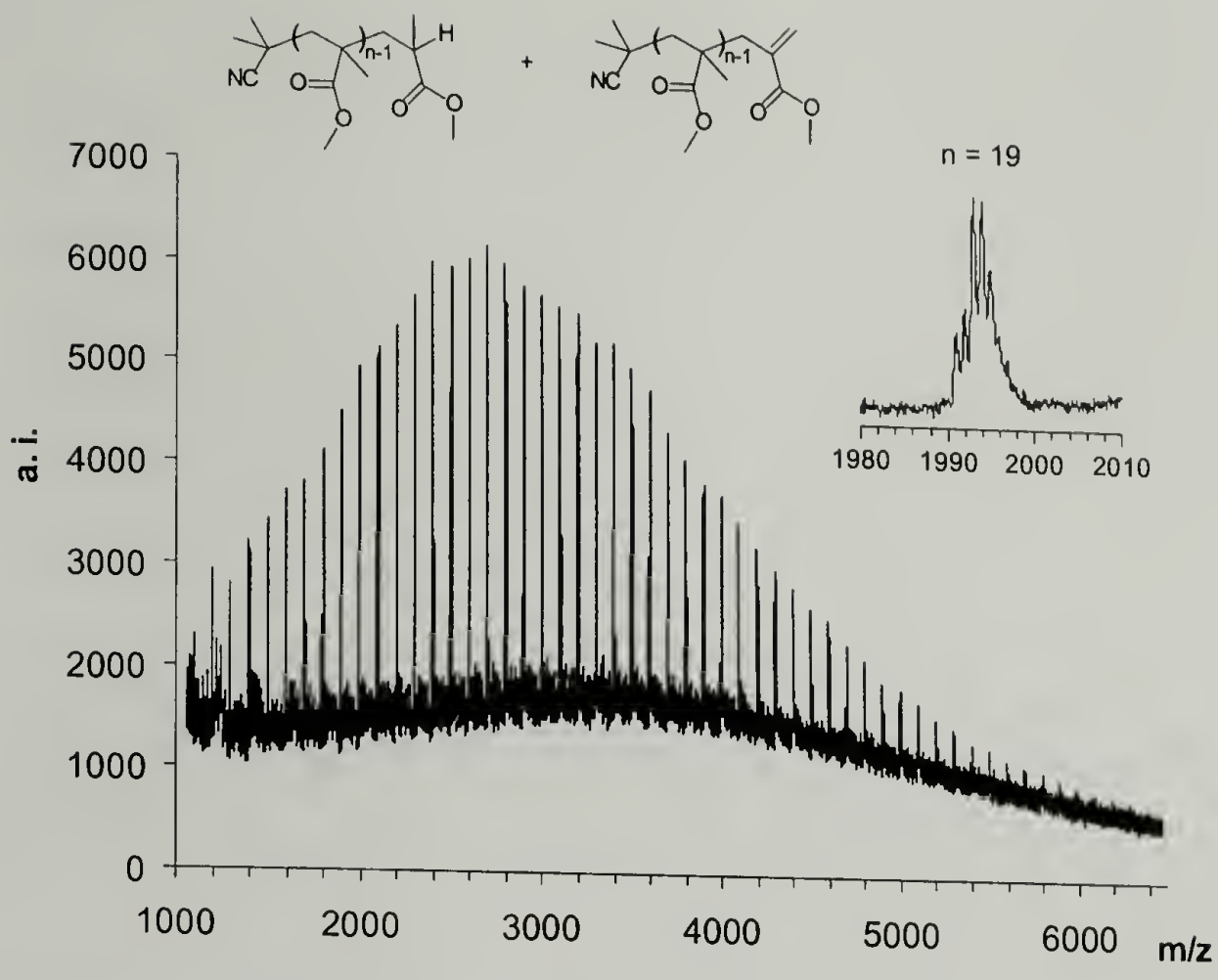


Figure A.1. MALDI-TOF spectrum of a PMMA sample obtained by RAFT polymerization.

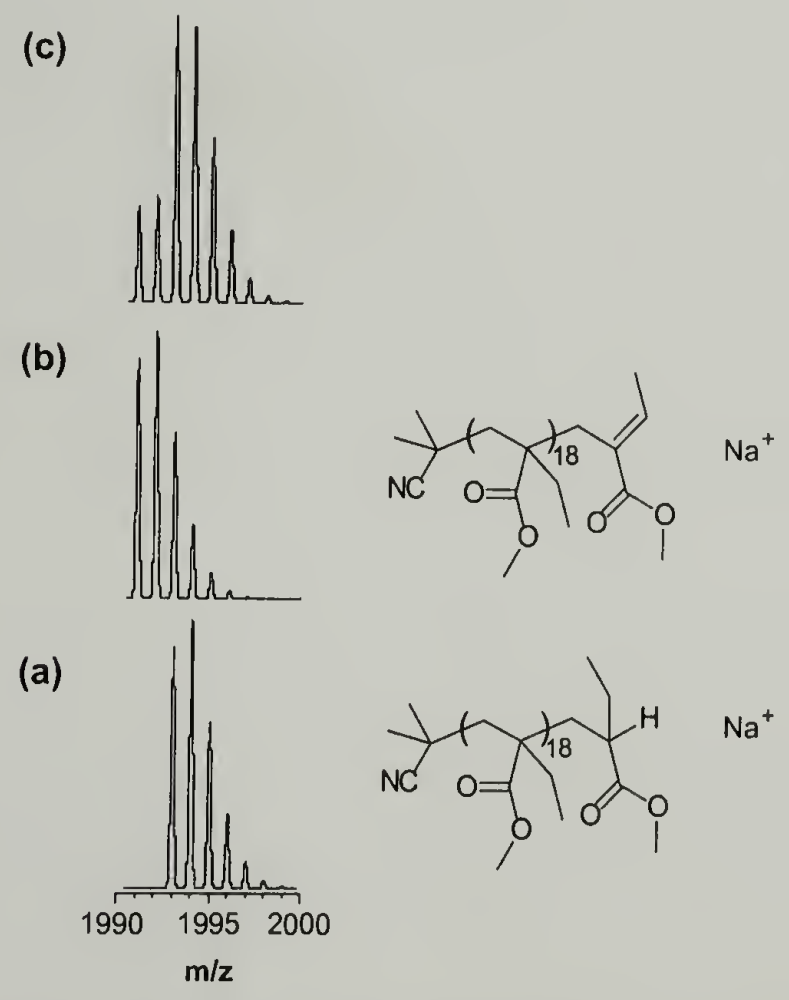
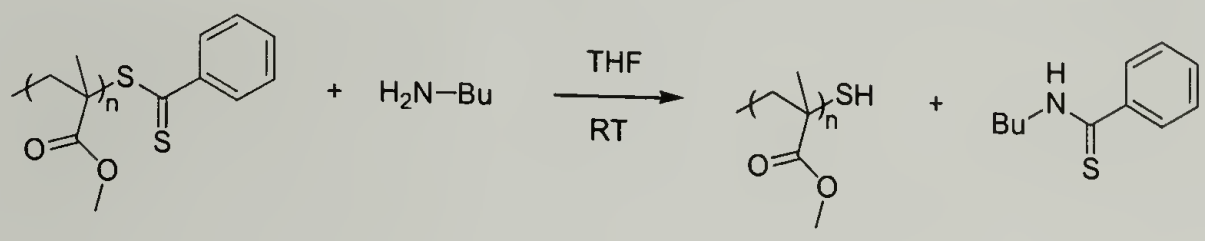


Figure A.2. Simulation of isotopic distributions of PMMA samples containing 19 repeating units: (a) H-terminated polymer, (b) C=C-terminated polymer, (c) mixture of the two above polymers in a 70:30 ratio.

ratios between the polymer chains. The simulation that provided the best fit with experimental data (Figure A.2c) used an intensity ratio of 70:30 between the hydrogen- and double-bond-terminated PMMAs.

Scheme A.2 Reaction of PMMA-dithiobenzoate with *n*-butylamine.



When a PMMA with dithiobenzoate end-groups was mixed with *n*-butyl amine in THF (PMMA = 100 mg, THF = 2 mL, *n*-butyl amine = 0.2 mL), the pink color characteristic of the dithioester functionality changed to a pale yellow within 20 seconds.

The MALDI-TOF spectrum of the polymer after a reaction time of 5 min is shown in Figure A.3 ,and clearly indicates the formation of a thiol end-group (major distribution, see Scheme A.2). A second, minor, distribution corresponds to disproportioned PMMAs, which probably originate from unreacted dithiobenzoate end-capped polymer chains. When the reaction was allowed to proceed for 30 min, the distribution corresponding to the thiol-terminated polymer almost disappeared, while the peaks assigned to the disproportionated polymer increased in intensity (Figure A.4). A close look at the isotopic distribution of these peaks revealed that the pattern was different from what would be observed for a disproportioned polymer (Figure A.1), with the distribution assigned to hydrogen-terminated PMMAs increasing in intensity. It seems reasonable that this increase in intensity corresponds to a thiolactone end-capped polymer resulting from a thiol-terminated PMMA by intramolecular backbiting on the closest methyl ester (Scheme A.3). Unfortunately, such thiolactone end-capped PMMAs have the same molar

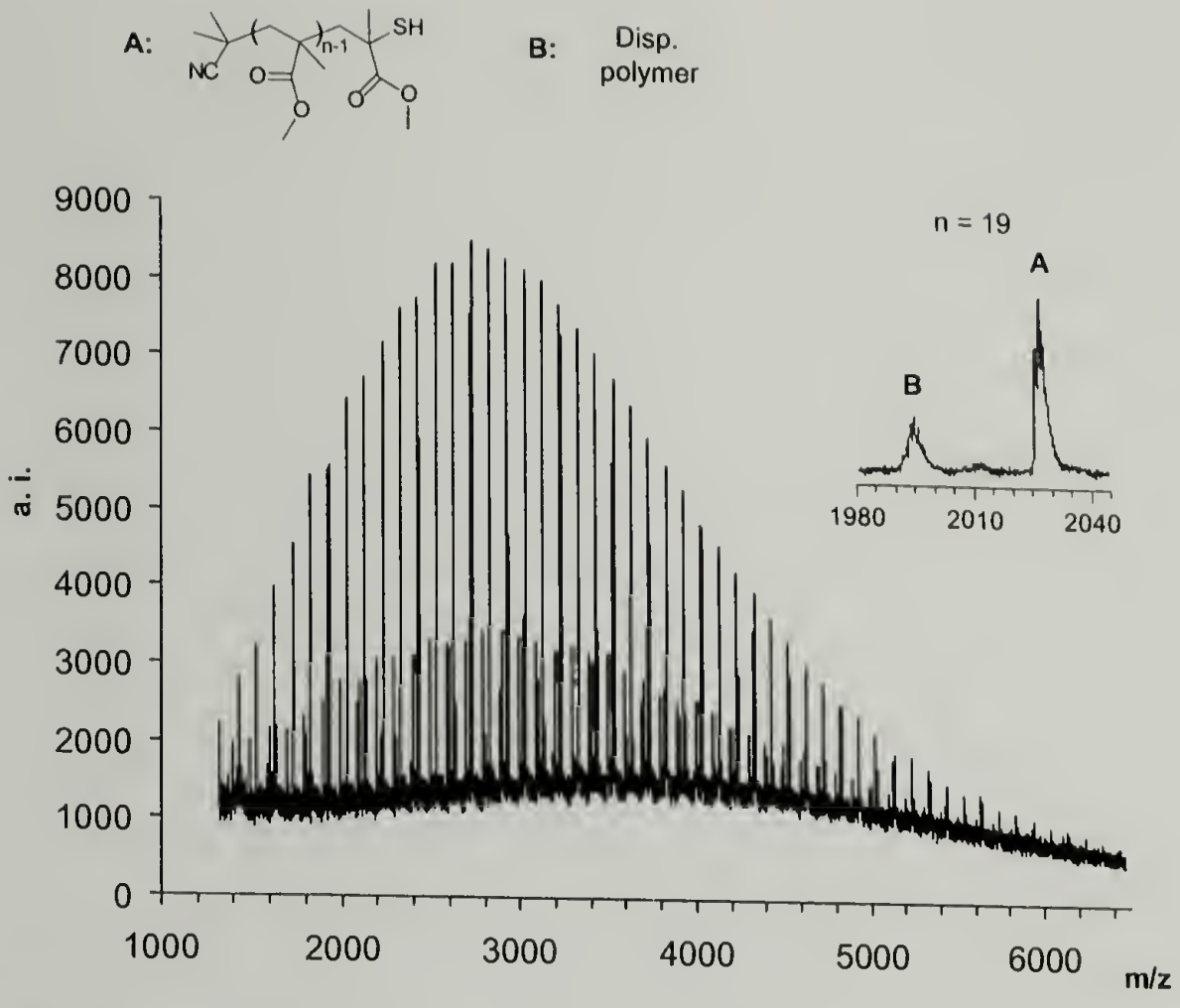


Figure A.3. MALTI-TOF spectrum of a PMMA obtained by RAFT polymerization and reacted with *n*-butyl amine for 5 min at room temperature.

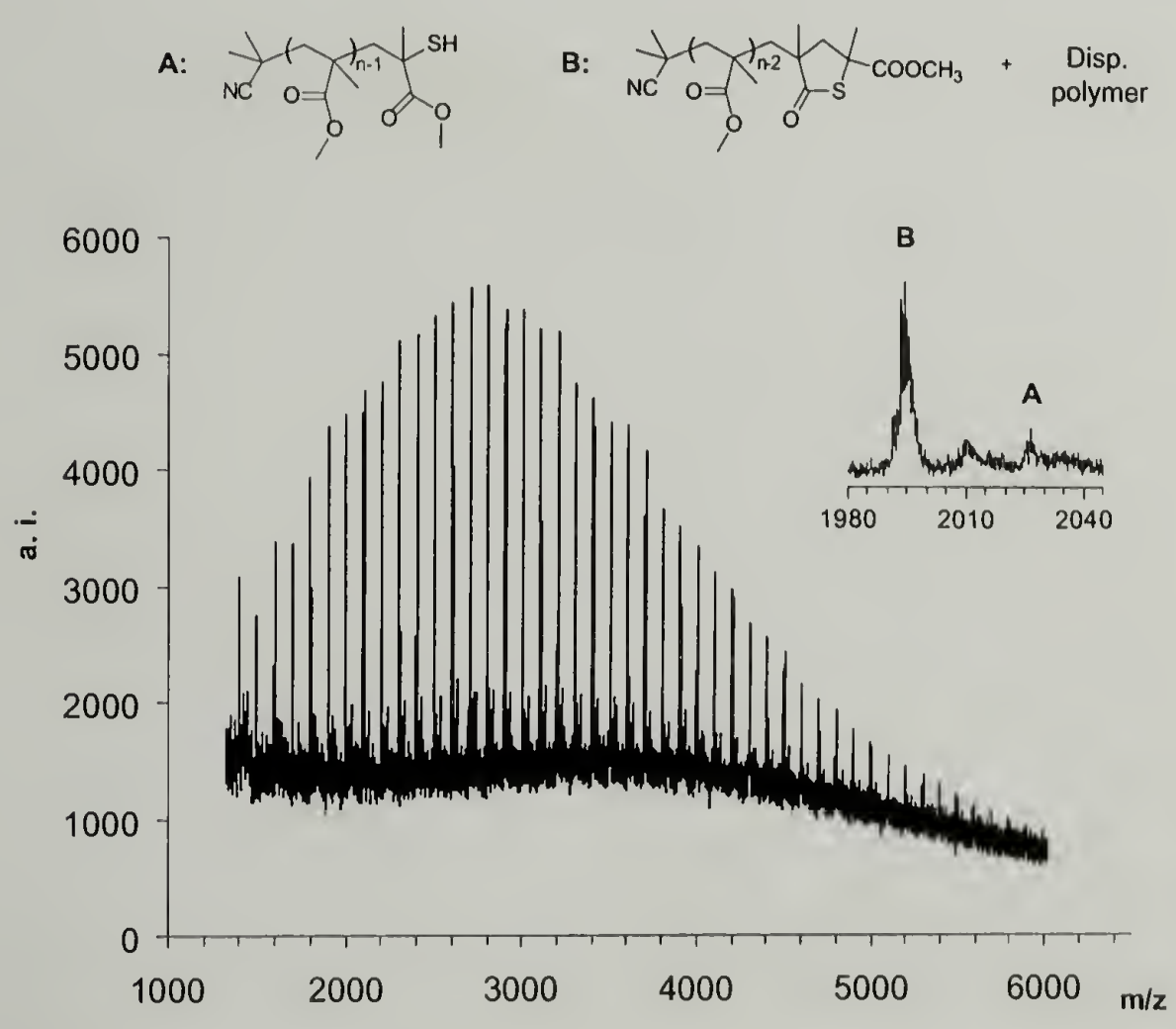
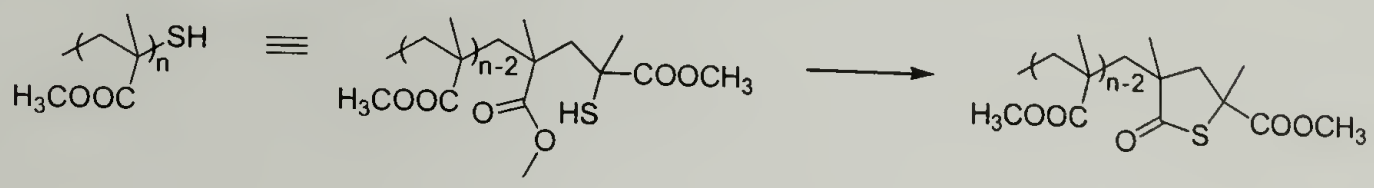


Figure A.4. MALTI-TOF spectrum of a PMMA obtained by RAFT polymerization and reacted with *n*-butyl amine for 30 min at room temperature.

mass and isotopic distribution as a hydrogen-terminated polymer, and therefore cannot be distinguished by MALDI. No other plausible mechanism explaining the experimental results could be identified, however.

Scheme A.3 Lactonization of thiol end-capped PMMA.



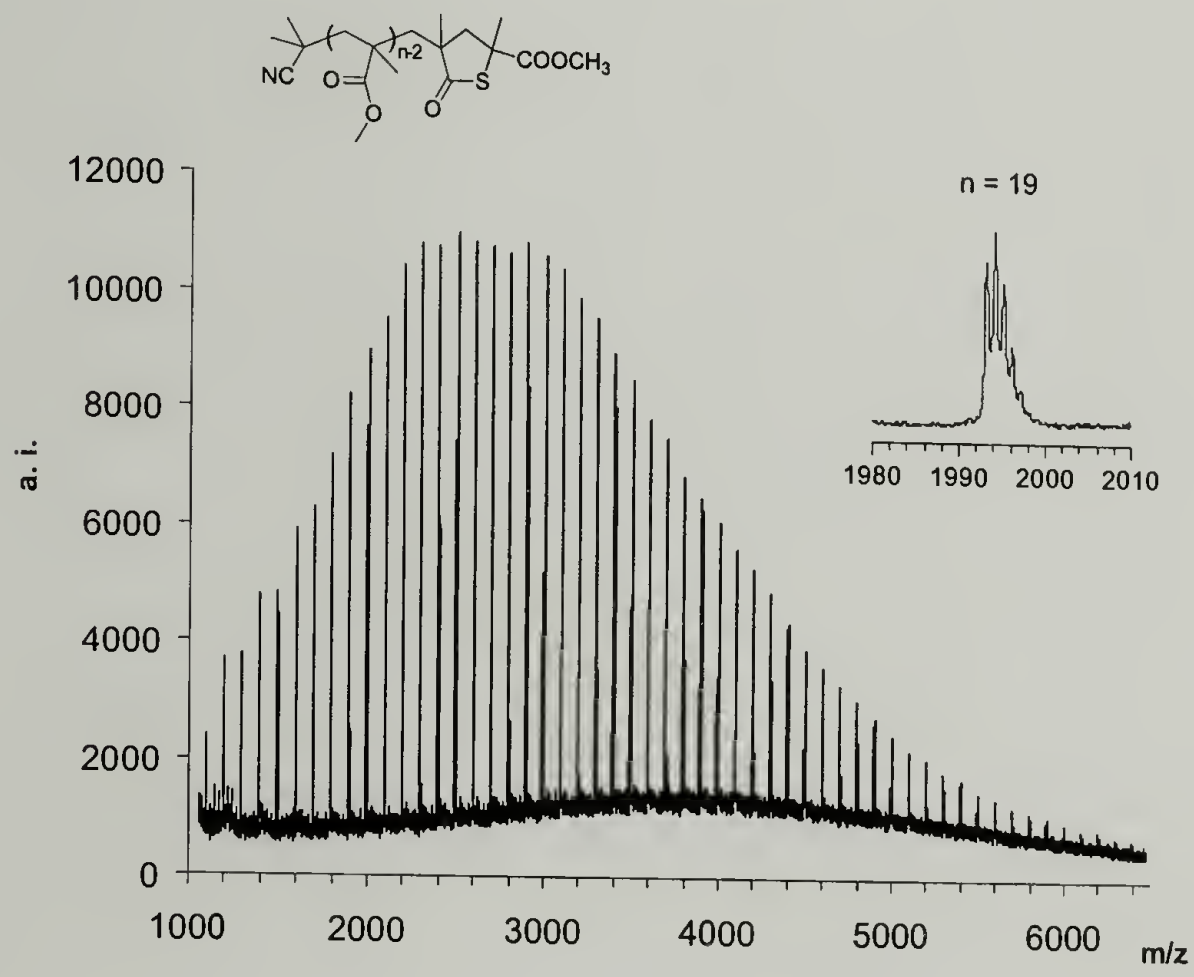


Figure A.5. MALDI-TOF spectrum of a PMMA synthesized by RAFT and reacted with *n*-butyl amine at 60 °C in the presence of allyl alcohol and AIBN.

In an attempt to trap the intermediate thiol end-groups by a reaction with an olefin, the above transformation was also performed in the presence of allyl alcohol and a catalytic amount of AIBN. The reaction was carried out for 16 hours at 60 °C in THF. The MALDI-TOF spectrum of the obtained polymer showed a single distribution, which

was assigned to a thiolactone end-capped PMMA (Figure A.5), with no additional signal corresponding to the disproportioned polymer. This result suggests that a clean conversion from a dithiobenzoate end-group to a thiol and then to a thiolactone had occurred, with the addition of the thiol end-groups to the olefinic double bond not fast enough to compete with the lactonization.

In conclusion, the transformation of dithiobenzoate end-groups on PMMA to thiols by reaction with primary amines proceeds rapidly at room temperature, but is followed by a fast intramolecular backbiting of the thiol end-group to the ester on the penultimate unit with the formation of a thiolactone. If thiol end-capped poly(methacrylate)s or poly(acrylates) are desired, the reaction should be stopped at an early stage, and subsequent transformations of the thiol groups should involve very efficient reagents able to compete with the fast intramolecular lactonization.

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